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(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract

    The present invention provides compounds which inhibit an envelope virus by inhibiting the fusion of the virus with the host cell. The virus may be inhibited in an infected cell, a cell susceptible of infection or a mammal in need thereof.

ANTI-VIRAL COMPOUNDS

Influenza viruses cause an infectious disease for which
there is no adequate therapeutic agent. The disadvantages of
5   existing treatments include the onset of clinical resistance
within thirty six hours and the ineffectiveness of the agents
against influenza B. Killed influenza virus vaccines have
been available for over sixty years. However, these vaccines
have not lessened the morbidity, mortality or severe financial
10   loss caused by this disease. It follows that an agent which
treats or prevents an influenza infection or is effective at
preventing the clinical symptoms associated with an influenza
infection will result in a significant benefit to society.
Currently, the only compounds approved for the
15   therapeutic and prophylactic treatment of influenza infections
are the adamantanes: amantadine and rimantadine. These
compounds inhibit influenza A by inhibiting the function of
the M2 ion channel activity of the virus. Amantadine is a
potent *in vitro* inhibitor of influenza A virus as demonstrated
20   by standard antiviral assays such as the plaque reduction
assay. Amantadine is effective in reducing the duration of
fever and other systemic complaints including but not limited
to myalgia (muscular ache) and fatigue when administered to
individuals infected with influenza A within forty-eight hours
25   of the onset of clinical symptoms. It has also been observed
that amantadine results in a one hundred-fold decrease of
virus titer in the nasal washes of human volunteers infected
with wild-type influenza virus which correlates with a
dramatic decrease in fever score. Thus, *in vitro* influenza
30   inhibition is predictive of useful *in vivo* effects, *i.e.* a
reduction of the clinical symptoms associated with the
influenza infection.
The present invention derives from the fact that
influenza is an enveloped virus which dictates that the virus
35   envelope must be fused with the endosomal membrane of the host
cell in order to initiate the process of introducing its
genetic information into the cell. Because this process is

common to all enveloped viruses, it is an attractive target for antiviral chemotherapy. Examples of envelope viruses which are inhibited according to the present invention include influenza, bovine diarrheal, hepatitis C, tick borne encephalitis and the like. The fusion domain of the envelope glycoprotein of influenza, hemagglutinin (HA) has been well-characterized. See, White J.M., Annu. Rev. Physiol. vol. 52, pages 675-697 (1990) which is herein incorporated by reference.

Influenza virus HA provides at least two distinct functions: 1) recognition of the host cell receptor, i.e., sialic acid residues on glycoconjugates, and 2) fusion of the viral envelope with the endosomal membrane. Both functions are essential for the propagation of influenza virus in vitro and in vivo. During viral maturation, monomeric HA is inserted into a lipid bilayer, post-translationally modified and oligomerized into a trimer of identical subunits (trimeric HA). The infectivity of the progeny virus is contingent upon a site-specific cleavage of HA by host cell protease(s). This cleavage results in the formation of two polypeptide chains, HA1 and HA2, which remain associated by non-covalent interactions as well as by an intermolecular and intramolecular disulfide bonds.

It has been established that influenza HA has two functionally relevant conformations. One conformation (Form A) exists as a metastable structure at neutral pH and mediates receptor recognition. Following receptor mediated binding to the host cell, the virus is transported to the endosomal compartment where it encounters an acidic environment. The low pH triggers a dramatic structural rearrangement of HA (Form A) which results in the formation of the other, more stable conformation of HA (Form B).

Form B of HA is required for fusion of the virus envelope with the endosomal membrane. It is the structural rearrangement from Form A to Form B of HA that allows the fusion domain of HA to directly interact with the endosomal membrane enabling the release of viral genetic information

into the host cell cytoplasm. These considerations lend themselves to the development of a strategy for antiviral intervention based on the abrogation of HA-mediated fusion of virus-host membranes. ;   .

5   The present invention relates to a compound of the formula:
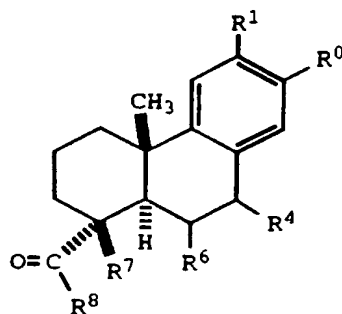
I

wherein:

R^0 and R^1 are independently hydrogen, hydroxy, C_1-C_6

10   alkyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6 alkyl), sulfhydryl, sulfamyl, $-SO_2-Cl$, $-S-C(O)-N(CH_3)_2$, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, C_1-C_4 alkylsulfonylamino, di(C_1-C_4 alkylsulfonyl)amino $-X^0-O-C(O)-C_1-C_4$ alkyl, $-O-(X^1)_i-X^2$, $-C(O)-X^3$, $-N-C(O)-R^2$ or $-O-R^3$;

15   X^0 is a bond or divalent(C_1-C_6 alkyl);

X^1 is an amino acid;

X^2 is hydrogen or an amino protecting group;

i is 1, 2 or 3;

X^3 is C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6 alkyl),

20   hydroxy(C_1-C_6 alkyl) or phenyl;

R^2 is C_1-C_4 alkyl, C_1-C_4 alkoxy, halo(C_1-C_4 alkyl), hydroxy(C_1-C_4 alkyl), phenyl, p-methoxy-phenyl, p-fluoro-phenyl, naphthyl, pyridyl, piperidinyl, thiazolyl, oxazolyl, thienyl, furyl, tetrahydrofuryl or cyclohexyl;

25   R^3 is C_1-C_6 alkenyl, $-CH_2-R^{3a}$, $-C(O)-R^{3b}$, $-C(S)-R^{3c}$, $-C(CH_3)_2C(O)NH_2$, phenyl or a group of the formula:

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R^{3a} is phenyl, p-fluorophenyl, pyridyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, N-(C$_1$-C$_4$ alkoxycarbonyl)piperidinyl, N-(trifluoromethyl)-piperidinyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, isooxazolyl, quinolyl, isoquinolyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, cyclohexyl, cyclopentyl, cyclopropyl or naphthyl;

R^{3b} is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, N-(C$_1$-C$_4$ alkoxycarbonyl)piperidinyl, N-(trifluoromethyl)piperidinyl, benzyloxy, pyridylmethyloxy, C$_1$-C$_6$ alkoxy, halo(C$_1$-C$_4$ alkoxy), amino, C$_1$-C$_4$ alkylamino or di(C$_1$-C$_4$ alkyl)amino;

R^{3c} is amino, C$_1$-C$_4$ alkylamino or di(C$_1$-C$_4$ alkyl)amino;

R^{3d} is oxygen, hydroximino, hydrazino or =CHZ;

Z is hydrogen, C$_1$-C$_4$ alkyl, halogen, di(C$_1$-C$_4$ alkyl)amino, C$_1$-C$_4$ alkoxycarbonyl, carbamoyl(C$_1$-C$_4$ alkyl), N-(C$_1$-C$_4$ alkyl)carbamoyl or N,N-di(C$_1$-C$_4$ alkyl)carbamoyl;

R^{3e} is hydrogen, nitro or trifluoromethyl;

X is a bond or -(CH$_2$)-;

R^4 is hydrogen, hydroxy, amino, C$_1$-C$_4$ alkylamino, di(C$_1$-C$_4$ alkyl)amino, C$_1$-C$_4$ alkoxy, =O, -O-S(CH$_3$)$_2$C(CH$_3$)$_3$, C$_2$-C$_6$ alkanoyloxy, N-(C$_2$-C$_6$ alkanoyl)amino, =N-R^5 or R^4 and R^6 combine to form a bond;

R^5 is hydroxy, amino, C$_1$-C$_4$ alkylamino, di(C$_1$-C$_4$ alkyl)amino, C$_1$-C$_4$ alkoxy, pyridylmethoxy, benzyloxy, piperazinyl, N-(methyl)piperazinyl or -O-CH$_2$-C(O)-R^{5a};

R^{5a} is hydroxy or C$_1$-C$_4$ alkoxy;

R^6 is hydrogen, halo, C$_1$-C$_4$ alkyl or =O;

R^7 is hydrogen or C$_1$-C$_4$ alkyl;

R^8 is hydroxy, halo, C$_1$-C$_6$ alkoxy, pyrrolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, morpholinyl or -N(R^9)-R^{10};

R^9 is hydrogen or methyl;

R^{10} is -(divalent C_1-C_6 alkyl)-R^{10a};

R^{10a} is pyridyl,

with the proviso that

i) when R^4 is hydrogen or $=O$; R^8 is methoxy; and R^1 is hydrogen; then R^0 cannot be hydrogen, hydroxy, isopropyl, methoxy, $-C(CH_3)_2OH$, $-C(O)CH_3$ or $-OC(O)CH_3$;

ii) when R^4 is hydrogen or $=O$; R^8 is methoxy; and R^0 is isopropyl; then R^1 cannot be hydroxy or methoxy;

iii) when R^4 is hydrogen or $=O$; R^8 is hydroxy; and R^0 is hydrogen; then R^1 cannot be hydrogen or isopropyl;

iv) when R^4 is hydrogen; R^8 is methoxy; and R^0 is hydrogen; then R^1 cannot be hydrogen, hydroxy, $-C(O)CH_3$ or $-OC(O)CH_3$;

or a pharmaceutically acceptable salt thereof.

The present invention provides new compounds of formula I, as described above, that are useful for treating or preventing a viral infection where the virus is an envelope virus that undergoes hemagglutinin-mediated fusion with a host cell and/or the resultant symptoms. These compounds, their pharmaceutically acceptable salts and the corresponding pharmaceutical formulations can be used alone or in combination with other antivirals, immunomodulators, antibiotics or vaccines.

All temperatures stated herein are in degrees Celsius (°C). All units of measurement employed herein are in weight units except for liquids which are in volume units.

The term "halo" represents chloro, fluoro, bromo or iodo.

The term "C_1-C_6 alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms. Typical
C_1-C_6 alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl and the like. The term "C_1-C_6 alkyl" includes within its definition the term "C_1-C_4 alkyl."

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The term "halo(C_1-C_6)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with 1, 2 or 3 halogen atoms attached to it. Typical halo(C_1-C_6)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-t-butyl, trifluoromethyl and the like.

The term "hydroxy(C_1-C_6)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with an hydroxy group attached to it. Typical hydroxy(C_1-C_6)alkyl groups include hydroxymethyl, 2-hydroxyethyl, 1-hydroxyisopropyl, 2-hydroxypropyl, 2-hydroxybutyl, 3-hydroxyisobutyl, hydroxy-t-butyl, hydroxypentyl and the like.

The term "C_1-C_4 alkylamino" represents a straight or branched alkylamino chain having from one to four carbon atoms attached to an amino group. Typical C_1-C_4 alkyl-amino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino and the like.

The term "di(C_1-C_4)alkylamino" represents a straight or branched dialkylamino chain having two alkyl chains, each having independently from one to four carbon atoms attached to a common amino group. Typical di(C_1-C_4)alkylamino groups include dimethylamino, ethylmethylamino, methylisopropyl-amino, t-butylisopropylamino, di-t-butylamino and the like.

The term "C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the term "C_1-C_4 alkoxy".

The term "C_2-C_6 alkenyl" represents a straight or branched alkenyl chain having from two to six carbon atoms. Typical C_2-C_6 alkenyl groups include ethenyl, propenyl, isopropenyl, buten-2-yl, t-butenyl, penten-1-yl·, hexen-3-yl, 3-methylpentenyl and the like.

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The term "C_1-C_4 alkoxycarbonyl" represents a straight or branched alkoxy chain having from one to four carbon atoms attached to a carbonyl moiety. Typical C_1-C_4 alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl and the like.

The term "carbamoyl(C_1-C_4)alkyl" represents a straight or branched alkyl chain having from one to four carbon atoms with a carbamoyl group attached to it. Typical carbamoyl(C_1-C_4)alkyl groups include carbamoylmethyl, carbamoylethyl, carbamoylpropyl, carbamoylisopropyl, carbamoylbutyl and carbamoyl-t-butyl and the like.

The term "N-(C_1-C_4)alkylcarbamoyl" represents a straight or branched alkyl chain having from one to four carbon atoms attached to the nitrogen atom of a carbamoyl moiety. Typical N-(C_1-C_4 alkyl)carbamoyl groups include N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, N-t-butylcarbamoyl and the like.

The term "N,N-di(C_1-C_4 alkyl)carbamoyl" represents a straight or branched alkyl chain having a straight or branched C_1-C_4 alkyl chain attached to each of the nitrogen atoms on a carbamoyl moiety. Typical N-(C_1-C_4)alkylcarbamoyl groups include N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-propyl-N-butylcarbamoyl, N,N-diisopropylcarbamoyl, N-methyl-N-butylcarbamoyl and the like.

The term "C_1-C_4 alkylsulfonylamino" represents a straight or branched alkyl group having from one to four carbon atoms attached to a sulfonylamino moiety. Typical C_1-C_4 alkylsulfonylamino groups include methylsulfonyl-amino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonyl-amino, butylsulfonylamino, isobutylsulfonylamino, sec-butylsulfonylamino and t-butylsulfonylamino.

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The term "di(C_1-C_4 alkylsulfonyl)amino" represents two
C_1-C_4 alkylsulfonyl moieties attached to an amino moiety.
Typical di(C_1-C_4 alkylsulfonyl)amino groups include
methylmethylsulfonylamino, ethylmethylsulfonylamino,
propylethylsulfonylamino, isopropylmethylsulfonylamino, t-
butylethylsulfonylamino, butylbutylsulfonylamino and the
like

The term "C_2-C_6 alkanoyl" represents a straight or
branched alkyl chain having from one to five carbon atoms
attached to a carbonyl moiety. Typical C_2-C_6 alkanoyl
groups include ethanoyl, propanoyl, isopropanoyl, butanoyl,
t-butanoyl, pentanoyl, hexanoyl, 3-methylpentanoyl and the
like.

The term "C_2-C_6 alkanoyloxy" represents a straight or
branched alkyl group having from one to five carbon atoms
attached to a carbonyloxy moiety. Typical C_2-C_6 alkanoyloxy
groups include ethanoyloxy, propanoyloxy, isopropanoyloxy,
butanoyloxy, isobutanoyloxy, sec-butanoyloxy, t-
butanoyloxy, pentanoyloxy and the like.

The term "C_2-C_6 alkanoylamino" represents a straight
or branched alkyl group one to five carbon atoms attached
to a carbonylamino moiety. Typical C_2-C_6 alkanoylamino
groups include ethanoylamino, propanoylamino,
isopropanoylamino, butanoyl-amino, isobutanoylamino, sec-
butanoylamino, t-butanoylamino, pentanoylamino and the
like.

As mentioned above, the invention includes the
pharmaceutically acceptable salts of the compounds defined
by formula I. Although generally neutral, a compound of
this invention can possess a sufficiently acidic, a
sufficiently basic, or both functional groups, and
accordingly react with any of a number of inorganic bases,
and inorganic and organic acids, to form a pharmaceutically
acceptable salt.

The term "pharmaceutically acceptable salt" as used
herein, refers to salts of the compounds of the above

formula which are substantially non-toxic to living
organisms. Typical pharmaceutically acceptable salts
include those salts prepared by reaction of the compounds
of the present invention with a mineral or organic acid or

5   an inorganic base. Such salts are known as acid addition
and base addition salts.

        Acids commonly employed to form acid addition salts
are inorganic acids such as hydrochloric acid, hydrobromic
acid, hydroiodic acid, sulfuric acid, phosphoric acid and

10   the like, and organic acids such as p-toluenesulfonic,
methanesulfonic acid, oxalic acid, p-bromophenylsulfonic
acid, carbonic acid, succinic acid, citric acid, benzoic
acid, acetic acid, and the like.

        Examples of such pharmaceutically acceptable salts are

15   the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite,
phosphate, monohydrogenphosphate, dihydrogenphosphate,
metaphosphate, pyrophosphate, chloride, bromide, iodide,
acetate, propionate, decanoate, caprylate, acrylate,
formate, isobutyrate, caproate, heptanoate, propiolate,

20   oxalate, malonate, succinate, suberate, sebacate, fumarate,
maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate,
chlorobenzoate, methylbenzoate, dinitrobenzoate,
hydroxybenzoate, methoxybenzoate, phthalate, sulfonate,
xylenesulfonate, phenylacetate, phenylpropionate,

25   phenylbutyrate, citrate, lactate, γ-hydroxybutyrate,
glycollate, tartrate, methanesulfonate, propanesulfonate,
naphthalene-1-sulfonate, napththalene-2-sulfonate,
mandelate and the like. Preferred pharmaceutically
acceptable acid addition salts are those formed with

30   mineral acids such as hydrochloric acid and hydrobromic
acid, and those formed with organic acids such as maleic
acid and methanesulfonic acid.

        Base addition salts include those derived from
inorganic bases, such as ammonium or alkali or alkaline

35   earth metal hydroxides, carbonates, bicarbonates, and the
like. Such bases useful in preparing the salts of this
invention thus include sodium hydroxide, potassium

hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

The term "amino-protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl groups, or urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, t-butoxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxy-carbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-

ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-
(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-
piperidyloxycarbonyl and the like; benzoylmethylsulfonyl,
2-nitrophenylsulfenyl, diphenylphosphine oxide and like
5   amino-protecting groups. The species of amino-protecting
group employed is not critical so long as the derivatized
amino group is stable to the condition of subsequent
reaction(s) on other positions of the intermediate molecule
and can be selectively removed at the appropriate point
10 without disrupting the remainder of the molecule including
any other amino-protecting group(s). Preferred amino-
protecting groups are t-butoxycarbonyl (t-Boc),
allyloxycarbonyl and benzyloxycarbonyl (CbZ). Further
examples of groups referred to by the above terms are
15 described by J. W. Barton, "Protective Groups in Organic
Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York,
N.Y., 1973, Chapter 2, and T. W. Greene, "Protective Groups
in Organic Synthesis", John Wiley and sons, New York, N.Y.,
1981, Chapter 7.
20   The term "carboxy-protecting group" as used in
the specification refers to substituents of the carboxy
group commonly employed to block or protect the carboxy
functionality while reacting other functional groups on the
compound. Examples of such carboxy-protecting groups
25 include methyl, p-nitrobenzyl, p-methylbenzyl, p-methoxy-
benzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-
trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl,
3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxy-
benzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, t-butyl, t-
30 amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-
trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-
butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β
(dibutylmethylsilyl)ethyl, p-toluenesulfonylethyl, 4-
nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-
35 (trimethylsilylmethyl)prop-1-en-3-yl and like moieties.
Preferred carboxy-protecting groups are allyl, benzyl and
t-butyl. Further examples of these groups are found in E.

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Haslam, "Protective Groups in Organic Chemistry", J.G.W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981, Chapter 5.

Preferred compounds are those compounds of formula I where:

R^0 is hydrogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6 alkyl), $-X^0$-O-C(O)-C_1-C_4 alkyl, -O-$(X^1)_i$-X^2, -C(O)-X^3 or -O-R^3;

R^1 is hydrogen, hydroxy, C_1-C_6 alkoxy, sulfhydryl, sulfamyl, $-SO_2$-Cl, amino, di(C_1-C_4 alkylsulfonyl)amino, -C(O)-X^3, -N-C(O)-R^2 or -O-R^3;

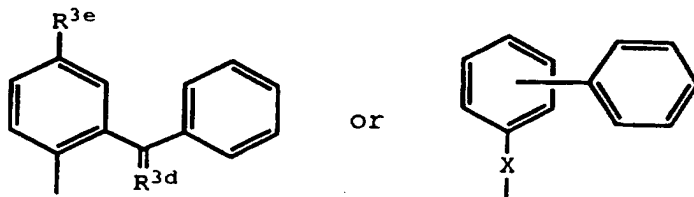X^0 is a bond or divalent(C_1-C_6 alkyl);

X^1 is an amino acid;

X^2 is hydrogen or an amino protecting group;

i is 1 or 2;

X^3 is C_1-C_6 alkyl;

R^2 is hydroxy(C_1-C_4 alkyl);

R^3 is C_1-C_6 alkenyl, $-CH_2$-R^{3a}, -C(O)-R^{3b}, -C(S)-R^{3c}, -C(CH$_3$)$_2$C(O)NH$_2$ or a group of the formula:

R^{3a} is phenyl, p-fluorophenyl, pyridyl, piperidinyl, piperazinyl or morpholinyl;

R^{3b} is piperidinyl, piperazinyl, morpholinyl, N-(C_1-C_4 alkoxycarbonyl)piperidinyl, N-(trifluoromethyl)piperidinyl, halo(C_1-C_4 alkoxy) or di(C_1-C_4 alkyl)amino;

R^{3c} is di(C_1-C_4 alkyl)amino;

R^{3d} is oxygen or hydroximino;

R^{3e} is hydrogen, nitro or trifluoromethyl;

X is a bond;

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R^4 is hydrogen, hydroxy, amino, =O, C$_2$-C$_6$ alkanoyloxy, =N-R^5 or -OSi(CH$_3$)$_2$;

R^5 is hydroxy, amino, di(C$_1$-C$_4$ alkyl)amino, C$_1$-C$_4$ alkoxy, pyridylmethoxy, -N-(methyl)piperazinyl or -O-CH$_2$-C(O)-R^{5a};

R^6 is hydrogen, chloro, bromo, methyl or =O;

R^7 is hydrogen or methyl;

R^8 is hydroxy, chloro, methoxy, 4-methylpiperazinyl or -N(R^9)-R^{10};

R^9 is hydrogen;

R^{10} is -CH$_2$-R^{10a}; and

R^{10a} is pyridyl;

or a pharmaceutically acceptable salt thereof.

Of these compounds, more preferred are those compounds of formula I where:

R^0 is hydrogen, hydroxy, C$_1$-C$_6$ alkoxy, -O-(X^1)$_i$-X^2, -X^0-O-C(O)-C$_1$-C$_4$ alkyl or -O-R^3;

R^1 is hydrogen, hydroxy, C$_1$-C$_6$ alkoxy or -O-R^3;

X^0 is a bond;

X^1 is an amino acid;

X^2 is hydrogen or an amino protecting group;

i is 1 or 2;

R^3 is C$_1$-C$_6$ alkenyl, -CH$_2$-R^{3a} or -C(O)-R^{3b};

R^{3a} is p-fluorophenyl or pyridyl;

R^{3b} is piperidinyl;

R^4 is hydrogen, hydroxy, =O or =N-R^5;

R^5 is hydroxy, dimethylamino or N-(methyl)piperazinyl;

R^6 is hydrogen, bromo or =O;

R^7 is methyl; and

R^8 is methoxy;

or a pharmaceutically acceptable salt thereof.

Of these compounds, even more preferred are those compounds of formula I where:

R^0 is hydrogen, hydroxy, C$_1$-C$_4$ alkoxy, -O-(X^1)$_i$-X^2,

-O-C(O)methyl or -O-R^3;

 R^1 is hydrogen, hydroxy, C$_1$-C$_4$ alkoxy or -O-R^3;

 X^1 is glycine, alanine or valine;

 X^2 is hydrogen, t-butoxycarbonyl or benzyloxycarbonyl;

 R^4 is =O or =N-R^5;

 R^5 is hydroxy;

 R^6 is hydrogen;

or a pharmaceutically acceptable salt thereof.

The compounds of formula I may be prepared according to procedures known in the art. For example, the following Reaction Schemes may be used, alone or in combination to provide the desired compounds. Once a reaction is complete, the intermediate compound may be isolated by procedures well-known in the art, for example, the compound may be crystallized and then collected by filtration, or the reaction solvent may be removed by extraction, evaporation or decantation. The intermediate compound may be further purified, if desired, by common techniques such as crystallization or chromatography over solid supports such as silica gel or alumina, before carrying out the next step of the reaction scheme.

The compounds of formula I where R^4 is =O or =N-R may be prepared according to the procedures shown below in Reaction Scheme I.

Reaction Scheme I

IA

1. Oxidation

2. Bromination

and

3. Reduction

and

4A. Hydrox-
amination

and

4B.

and
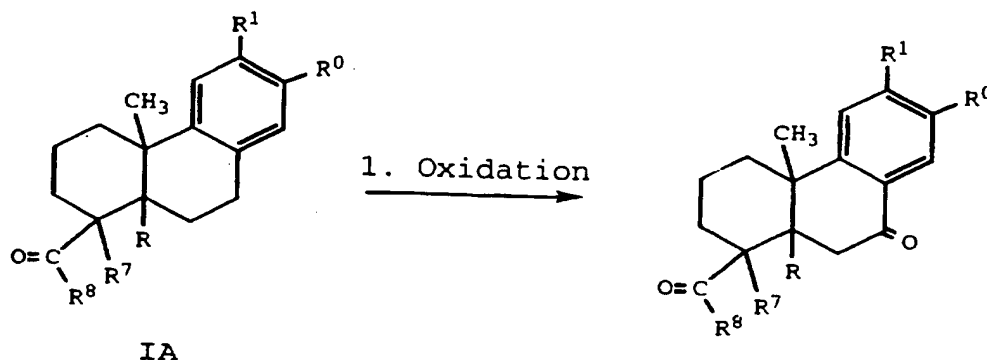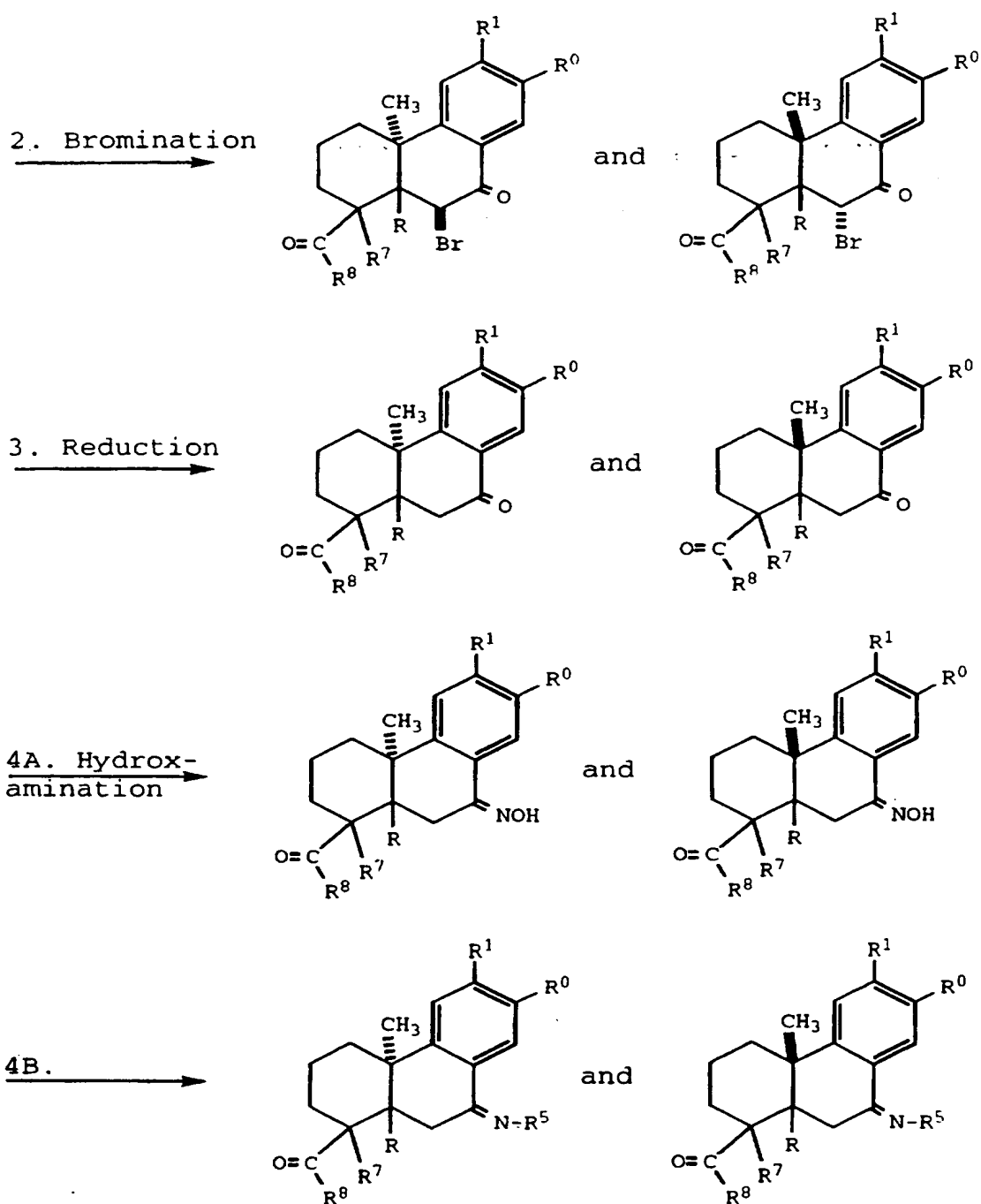
where Reactions I.4A and 4B represent alternative reactions
that follow Reaction I.3.

    Reaction scheme I is accomplished by carrying out
reactions 1-4 is sequential order. Reaction I.1 is carried
out by oxidizing a compound of formula IA, for example, by

reaction with chromium trioxide in an acetic acid/water mixture, to provide the corresponding ketone. The chromium trioxide is generally employed in an amount ranging from equimolar proportions to about a 4 molar excess relative to the compound of formula IA, preferably in about a 2-4 molar excess. The acetic acid/water mixture is generally a 10:1 to a 2:1 mixture of acetic acid to water, preferably about 4:1. The reaction is generally substantially complete after about 1 to 10 hours when conducted at a temperature of from about 23°C to about 60°C. The reaction is preferably conducted at a temperature of from about 23°C to about 30°C for about 5 to 10 hours.

In Reaction I.2, the ketone obtained from Reaction I.1 is reacted with bromine in a suitable solvent such as diethyl ether, tetrahydrofuran or dimethoxyethane, to provide a mixture of bromoketones which are then separated using standard separation techniques such as chromatography. These isomerically pure bromoketones are then used to prepare various isomerically pure compounds of formula I. The bromine is generally employed in an amount ranging from about equimolar proportions to about a 2 molar excess relative to the ketone reactant, preferably in about a 1-1.5 molar excess. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. The reaction is generally substantially complete after about 1 to 3 hours when conducted at a temperature of from about 23°C to about 30°C. The reaction is preferably conducted at room temperature for about 1 to 1.5 hours.

Alternatively, the ketone obtained from Reaction I.1 is reacted with a silylating agent in the presence of a base in a suitable solvent such as methylene chloride, diethyl ether or tetrahydrofuran to provide the corresponding silylated enol ether. Preferred bases include 2,6-lutidine and collidine. A preferred silylating agent is t-butyldimethylsilyl trifluoromethanesulfonate.

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The silylating agent is generally employed in an amount
ranging from about equimolar proportions to about a 2 molar
excess relative to the ketone reactant, preferably in about
a 1-1.5 molar excess. Solvent choice is not critical so
long as the solvent employed is inert to the ongoing
reaction and the reactants are sufficiently solubilized to
effect the desired reaction. The reaction is generally
substantially complete after about 30 minutes to 2 hours
when conducted at a temperature of from about 0°C to about
50°C. The reaction is preferably conducted at a
temperature of from about 10°C to about 25°C for about
30 minutes to about 1 hour.

        The silylated enol ether is then reacted with bromine
substantially as described above with the exception that
the reaction is carried out in the presence of acetic acid.
Typical solvents suitable for use in this reaction include
any organic solvent such as methylene chloride, diethyl
ether or tetrahydrofuran. Solvent choice is not critical
so long as the solvent employed is inert to the ongoing
reaction and the reactants are sufficiently solubilized to
effect the desired reaction.

        In Reaction I.3, the bromoketone is reduced, for
example by reaction with zinc dust and sodium acetate in
glacial acetic acid, to provide the corresponding ketones.
The zinc is generally employed in an amount ranging from
about equimolar proportions to about a 4 molar excess
relative to the ketone reactant, preferably in about a 1.5-
3 molar excess. The sodium acetate is generally employed
in an amount ranging from about 0.6 molar equivalents to
about 1.2 molar equivalents relative to the ketone
reactant. The reaction is generally substantially complete
after about 1 to 10 hours when conducted at a temperature
of from about 60°C to the reflux temperature of the
mixture. The reaction is preferably conducted at reflux
temperature for about 1 to 2 hours.

        Alternatively, hydroxylamine hydrochloride is reacted
with sodium acetate in a suitable solvent such as ethanol.

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The sodium acetate is generally employed in an amount
ranging from about 1.1 molar equivalents to about a 50
molar excess relative to the hydroxylamine. The reaction
is generally substantially complete after about 1 to 72
5   hours when conducted at a temperature of from about 25°C to
about 80°C. The reaction is preferably conducted at a
temperature in the range of from about 25°C to about 30°C
for about 5 to 24 hours.

In Reaction I.4A, the ketone obtained from Reaction
10   I.3 is reacted with hydroxylamine hydrochloride in a
mixture of methanol, water and acetic acid to provide the
desired oxime compound. The hydroxylamine hydrochloride is
generally employed in an amount ranging from about
equimolar proportions to about a 4 molar excess relative to
15   the ketone reactant, preferably in about a 1.3-3 molar
excess. The ratio of methanol to water to acetic acid is
generally 10-20:1:0.1, preferably 15:1:0.1. The reaction
is generally substantially complete after about 1 hour to
about 2 days when conducted at a temperature of from about
20   40°C to the reflux temperature of the mixture. The
reaction is preferably conducted at reflux temperature for
about 1 to 6 hours.

In Reaction I.4B, the ketone obtained from Reaction
I.3 is reacted with an hydrazine hydrochloride such as 1-
25   amino-4-methylpiperazine, 1,1-dimethylhydrazine or
hydrazine in the presence of a base in an inert solvent at
a temperature of from about 25°C to 80°C for 2 to 24 hours.
Typical bases include sodium acetate, potassium hydroxide,
triethylamine and the like. Suitable solvents include
30   ethanol, isopropanol and dimethylformamide. Solvent choice
is not critical so long as the solvent employed is inert to
the ongoing reaction and the reactants are sufficiently
solubilized to effect the desired reaction.

The phenyl moiety of the compounds of formula I
35   prepared above may be substituted according to Reaction
Scheme II, as follows.

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Reaction Scheme II
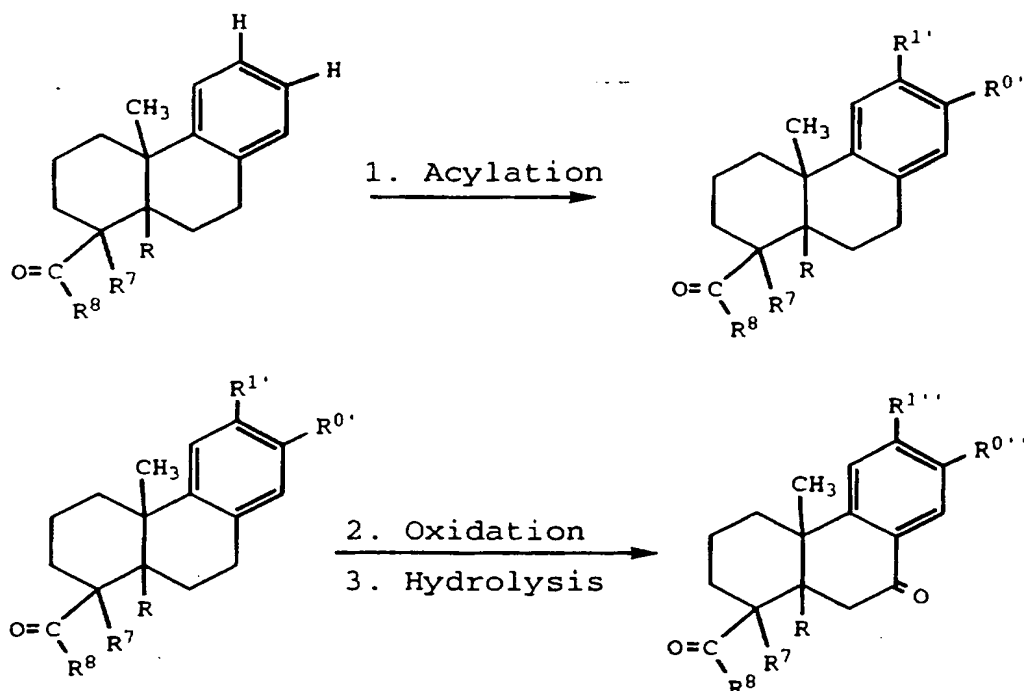
where $R^{0'}$ and $R^{1'}$ are independently hydrogen or $-C(O)CH_3$; and $R^{0''}$ and $R^{1''}$ are independently hydrogen or hydroxy.

In Reaction II.1, the compound of formula I where R^0 and R^1 are each hydrogen is subjected to a Friedel-Crafts acylation by reacting the compound of formula I with an acid halide, in the presence of a catalyst in an inert solvent such as carbon disulfide. The acid halide is generally employed in an amount ranging from about equimolar proportions to about a 1.5 molar excess relative to the compound of formula I, preferably in about a 1.1-1.3 molar excess. Preferred acid halides include acetyl chloride, acetyl bromide or the like. Preferred catalysts include aluminum trichloride, aluminum tribromide or the like. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. The reaction is generally substantially complete after about 1 to 10 hours when conducted at a temperature of from about 50°C to the reflux temperature of

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the mixture. The reaction is preferably conducted at reflux temperature for about 1 to 2 hours.

In Reaction II.2, the acylated compound of formula I obtained from Reaction II.1 is oxidized to provide the corresponding phenol in a two step reaction. First, the acyl moiety is reacted with a peracid in the presence of an acid catalyst in an inert solvent such as dimethoxyethane to provide the corresponding ester with is then reacted with sodium bicarbonate in an alcohol/water mixture to provide the desired phenol.

The peracid is generally employed in an amount ranging from about equimolar proportions to about a 2 molar excess relative to the acyl moiety, preferably in about a 1-1.3 molar excess. The amount of catalyst typically employed is in the range of 0.005-0.04 equivalents relative to the acyl moiety. A preferred peracid is metachloro-peroxybenzoic acid. A preferred catalyst is p-toluenesulfonic acid. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. The reaction is generally substantially complete after about 1 to 10 hours when conducted at a temperature of from about 50°C to the reflux temperature of the mixture. The reaction is preferably conducted at reflux temperature for about 1 to 3 hours.

The resultant ester is typically refluxed with a base in a methanol/water mixture for about 1 to 7 hours to provide the desired phenol compound. Preferred bases include sodium bicarbonate, sodium carbonate, sodium hydroxide or potassium hydroxide or the like. The base is generally employed in an excess, for example from about a 1 molar excess to about a 6 molar excess relative to the ester moiety, preferably in about a 2-5 molar excess.

The phenol compounds obtained from Reaction Scheme II may be used to prepare various substituted compounds of formula I, as described below.

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For example, the hydroxy moiety may be alkylated by
reacting the phenol compound with a suitable alkylating
agent in the presence of a base in an inert solvent.
Examples of bases include triethylamine, diisopropyl
ethylamine, sodium hydride and potassium carbonate.
Typical solvents include methylene chloride,
tetrahydrofuran, dimethylformamide and the like. Solvent
choice is not critical so long as the solvent employed is
inert to the ongoing reaction and the reactants are
sufficiently solubilized to effect the desired reaction.
Suitable alkylating agents include iodomethane, allyl
iodide, p-fluorophenyl bromide, 3-bromomethyl-pyridine and
2-fluorobenzophenone and the like. The reaction is
generally substantially complete after about 1 to 20 hours
when conducted at a temperature of from about 0°C to 170°C.
The reaction is preferably conducted at a temperature of
from about 25°C to about 80°C for about 4 to 16 hours.

Alternatively, the hydroxy moiety may be alkylated by
reacting the phenol with an alcohol in the presence of
triphenylphosphine and a suitable activating agent in an
inert solvent, such as tetrahydrofuran or ethylene glycol
dimethyl ether. Examples of suitable activating agents
include diethyl azodicarboxylate, dimethyl
azodicarboxylate, diisopropyl azodicarboxylate and the
like. Examples of alcohols include 3-pyridyl carbinol, N-
t-butoxycarbonyl-3-piperidinemethanol and the like. The
reaction is generally substantially complete after about
0.5 to 2 hours when conducted at a temperature of from
about 0°C to 85°C. The reaction is preferably conducted at
a temperature of from about 25°C to about 70°C for about 30
minutes to 1 hour.

The hydroxy moiety may be converted to an ester or a
carbonate by reacting the phenol with an acylating agent in
the presence of a base in an inert solvent, such as
methylene chloride, tetrahydrofuran or dimethylformamide.
Typical bases include triethylamine, diisopropyl
ethylamine, sodium hydride and the like. Typical acylating

agents include N-(t-butoxycarbonyl)-4-chlorocarbonyl
piperdine, 2,2,2-trichloroethyl chloroformate, N-(t-
butoxycarbonyl)-hydroxybenzotriazole amino esters. The
reaction is generally substantially complete after about 1
to 20 hours when conducted at a temperature of from about
0°C to 60°C. The reaction is preferably conducted at a
temperature of from about 10°C to about 25°C for about 1 to
5 hours.

The hydroxy moiety may be converted to the
corresponding aniline in a three step reaction. First, the
phenol is reacted with a suitably substituted amide such as
2-methyl-2-bromo-propanamide in the presence of a base such
as sodium hydride or triethylamine in an inert solvent,
such as dioxane or tetrahydrofuran at a temperature of 25°C
to 100°C to provide the corresponding amido-ether. This
amido-ether is then reacted with sodium hydride in an inert
solvent such as dimethylformamide, 1,3-dimethyl-3,4,5,6-
tetrahydro-2(1H)-pyrimidone or a mixture thereof at
temperatures ranging from 25°C to 145°C to provide the
rearranged amido-alcohol. Finally, the amido-alcohol is
reacted with an acid, such as hydrochloric acid in dioxane
at 50°C to 100°C to provide the desired aniline.

The aniline may be converted to the corresponding
sulfonamide by reacting the aniline with a sulfonyl
chloride such as methanesulfonyl chloride or
isopropylsulfonyl chloride in the presence of a base, such
as triethylamine, diisopropyl ethylamine or sodium hydride
at a temperature of from about 0°C to 50°C in an inert
solvent, such as methylene chloride, tetrahydrofuran or
dimethylformamide.

The hydroxy moiety may be converted to a thiophenol in
a three step reaction. First the phenol is reacted with a
thio-carbamoyl (for example dimethylthiocarbamoyl chloride)
in the presence of a base in an suitable solvent, such as
water or dimethylformamide at a temperature ranging from
25°C to 50°C for 1 to 3 hours to provide the oxo-
thiocarbamate. Typical bases include potassium hydroxide,

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triethylamine and the like. The oxo-thiocarbamate is
converted to the corresponding thio-oxocarbamate compound
by isolating and heating the neat solid to its melting
point. Finally, the thio-oxocarbamate is reacted with a
5   base, such as potassium hydroxide or sodium hydroxide in an
alcoholic solvent, such as methanol or ethanol at a
temperature of 20°C to 80°C for 20 minutes to 1 hour to
provide the corresponding thiophenol.

The thiophenol may be converted to the corresponding
10   sulfonamides by reacting the thiophenol with an oxidizing
agent (for example, potassium nitrate) in an inert solvent
such as acetonitrile, followed by the addition of a
chlorinating agent (for example, sulfuryl chloride) at
temperatures ranging from 0°C to 25°C to provide a mixture
15   of sulfonyl chlorides which are separable using standard
chromatographic techniques. These sulfonyl chlorides may be
converted to the desired sulfonamides by reaction with an
appropriately substituted amine such as ammonium hydroxide,
methylamine, isopropylamine or benzylamine at a temperature
20   of from about 0°C to 40°C in an inert solvent such
tetrahydrofuran.

The hydroxy moiety may be converted to the
corresponding amino esters by reacting the phenol with an
amino protected amino acid in the presence of a coupling
25   reagent and a catalyst in an inert solvent such as diethyl
ether, tetrahydrofuran or methylene chloride. Preferred
amino protecting groups include t-butoxycarbonyl or
benzyloxycarbonyl. The amino reactant is generally
employed in equimolar proportions to a slight excess
30   (1.3 equivalents) relative to the phenol reactant in the
presence of an equimolar quantity to a slight excess
(1.5 equivalents) of the coupling reagent. Typical
coupling agents include dicyclohexylcarbodiimide (DCC), 1-
(3-dimethylaminopropyl)-3-ethylcarbodiimide, benzotriazol-
35   1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
(BOP), N,N'-diethylcarbodiimide, carbonyldiimidazole, bis(2-
oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) or N-

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ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) and the
like. Preferred coupling agents include DCC and BOP.
Typical catalysts include DMAP and 4-pyrrolopyridine. The
reaction is substantially complete in 1 to 10 hours when
5   carried out at a temperature of from about -30°C to about
35°C, preferably from about 0°C to about 25°C.

The starting materials used in the procedures detailed
above may be obtained commercially or prepared according to
procedures known in the art. For example, the compounds of
10   formula IA:
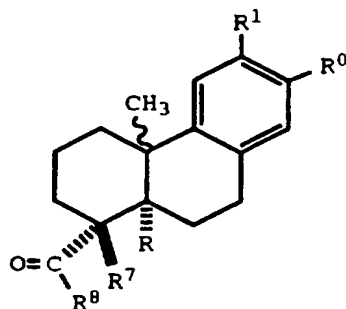
IA

may be prepared substantially in accordance with the
procedure detailed in Ohta and Ohmuri, Chem. Pharm. Bull.
(Tokyo), vol 5, page 91 (1957). The isomeric mix of
15   compounds may be separated using standard separation
techniques such as recrystallization or column
chromatography or may be subjected to the bromination
methodology described above in Reaction Scheme I.
Preferably, these isomers are obtained using the
20   bromination methodology described above in Reaction
Scheme I.

The following Preparations and Examples further
illustrate specific aspects of the present invention. It
is to be understood, however, that these examples are
25   included for illustrative purposes only and are not
intended to limit the scope of the invention in any respect
and should not be so construed.

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<u>Example 1</u>
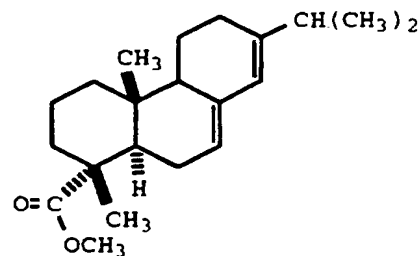
5   To a solution of NaOMe (prepared in situ from 2.6 g of
sodium in 400 ml of anhydrous MeOH (0.108 mol), under N_2),
was added 15.0 g (0.035 mol) of 70% abietic acid. After
stirring the mixture for 10 minutes, 14.0 ml (0.22 mol) of
iodomethane was added and the mixture was refluxed for 24

10   hours, cooled and concentrated in vacuo to provide a
residue which was dissolved in 500 ml of EtOAc, washed
sequentially with 500 ml of a saturated $NaHCO_3$ solution and
a saturated sodium chloride solution (NaCl), dried over
Na_2SO_4, filtered and concentrated in vacuo. The crude

15   material was purified using flash chromatography (eluent of
2% EtOAc in hexanes).
Yield: 10.0 g of a dark yellow oil (90.4%).
IR($CHCl_3$): 2952, 1718 and 1251 cm^{-1}.
^1H NMR (300MHz, $CDCl_3$): δ5.78 (s, 1H); 5.38 (brs, 1H);

20   3.66 (s, 3H); 2.17-2.30 (m, 3H); 1.68-2.16 (m, 8H); 1.50-
1.65 (m, 2H); 1.26 (s, 3H); 1.24 (m, 2H); 1.02 (d, J=2.6Hz,
3H); 1.00 (d, J=2.6Hz, 3H) and 0.83 (s, 3H).
MS(FD): m/e 316(M+).
Elemental Analysis for $C_{21}H_{32}O_2$:

25   Calcd: C, 79.70; H, 10.19;
         Found: C, 79.49; H, 9.94.

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Example 2
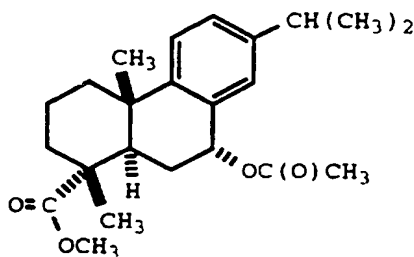
To a mixture of 5.0 g (15.8 mmol) of the compound in
Example 1 in 100 ml of acetic anhydride, was added 2.5 g
(22.5 mmol) of selenium (IV) oxide, under N_2. The reaction
mixture was warmed to 70°C, stirred for 16 hours, cooled,
filtered and then diluted to 500 ml with CH_2Cl_2. The
resulting layers were separated and the organic layer was
washed with 500 ml of NaCl, dried over Na_2SO_4, filtered and
then concentrated in vacuo to provide a dark yellow solid.
This solid was purified using flash chromatography (eluent
of 5% EtOAc in hexanes) to provide two major fractions.

The first fraction was concentrated to provide 537 mg
of an oil. This oil was hydrogenated with 135 mg of 5%
Pd/C in 25 ml of MeOH (8 hours, room temperature, 6.0 psi).
The reaction mixture was filtered and the filtrate
concentrated in vacuo. The crude material was purified
using flash chromatography (eluent of 2% EtOAc in hexanes)
to provide the compound of Example 3 (400 mg of a clear oil
(75%) m.p. 50°C). The second fraction was concentrated in
vacuo to provide the compound.

Yield: 2.8 g of a light yellow solid (47%).
m.p. 165-167°C.
IR (KBr): 2956, 1722 and 1251 cm^{-1}.
^{1}H NMR (300MHz, CDCl$_3$): δ7.23 (m, 2H); 7.04 (d, J=1.8Hz,
1H); 5.90 (m, 1H); 3.64 (s, 3H); 2.86 (m, 1H); 2.60 (dd,
J=1.5,11.0Hz, 1H); 2.31 (d, J=12.1Hz, 1H); 2.08 (s, 3H);
2.07 (m, 1H); 1.60-1.80 (m, 6H); 1.26 (s, 3H); 1.24 (s,
3H); 1.22 (s, 3H) and 1.19 (s, 3H).
MS(FD): m/e 372(M+).

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Elemental Analysis for $C_{23}H_{32}O_4$:

      Calcd: C, 74.16; H, 8.66;

      Found: C, 74.44; H, 8.71.

5
<div style="text-align:center"><u>Example 3</u></div>
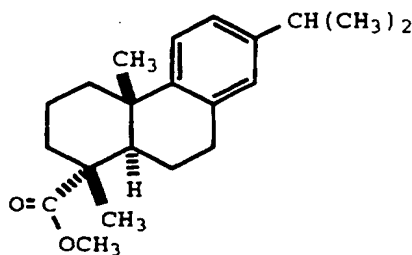
To a mixture of 23.6 g (0.063 mmol) of the compound in
Example 2 in 1500 ml of MeOH, was added 5.8 g of 10% Pd/C

10   and 5.8 g (0.030 mmol) of p-toluenesulfonic acid
monohydrate. The reaction mixture was reacted for 16 hours
at room temperature, 60 psi, filtered and then concentrated
in vacuo to provide a residue. This residue was dissolved
in 700 ml of EtOAc, washed sequentially with 700 ml of

15   saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4,
filtered and then concentrated in vacuo.
Yield: 19.3 g (97.5%) of an oil.
IR ($CHCl_3$): 2955, 1718 and 1254 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ7.16 (d, J=8Hz, 1H); 7.00 (d,

20   J=8Hz, 1H); 6.88 (s, 1H); 3.66 (s, 3H); 2.80-2.90 (m, 3H);
2.23-2.32 (m, 2H); 1.35-1.90 (m, 7H); 1.28 (s, 3H); 1.24
(s, 3H) and 1.21 (s, 6H).
MS(FD): m/e 314(M+).
Elemental Analysis for $C_{21}H_{30}O_2$:

25   Calcd: C, 80.21; H, 9.62

        Found: C, 80.34; H, 9.73

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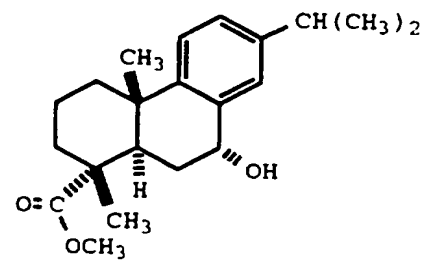
Example 4

     To a suspension of 185 mg (0.50 mmol) of the compound
5 of Example 2 in 10 ml of MeOH, was added 5 ml (0.50 mmol)
   of 0.1N NaOH. The reaction mixture was refluxed for 2
   hours, cooled and partitioned between 50 ml of EtOAc and
   50 ml of 0.2N HCl. The resulting layers were separated and
   the organic layer was washed with 50 ml of a saturated NaCl
10 solution, dried over Na_2SO_4, filtered and then concentrated
   in vacuo to provide a yellow oil. This oil was purified
   using flash chromatography (eluent of 10% EtOAc in
   hexanes).
   Yield: 158 mg of a clear oil (96%).
15 m.p. 105-107°C.
   IR (KBr): 2957, 3500 and 1719 cm^{-1}.
   ^1H NMR (300MHz, $CDCl_3$): δ 7.20 (m, 3H); 4.75 (t, J=4.8Hz,
   1H); 3.69 (s, 3H); 2.88 (m, 1H); 2.50 (dd, J=1.8,13.2Hz,
   1H); 2.30 (brd, J=12.1Hz, 1H); 2.06-2.17 (m, 1H); 1.98 (d,
20 J=7.0Hz, 1H); 1.69-1.84 (m, 4H); 1.55 (m, 2H); 1.29 (s,
   3H); 1.25 (s, 3H); 1.23 (s, 3H) and 1.17 (s, 3H).
   MS(FD): m/e 330(M+).

Example 5

25
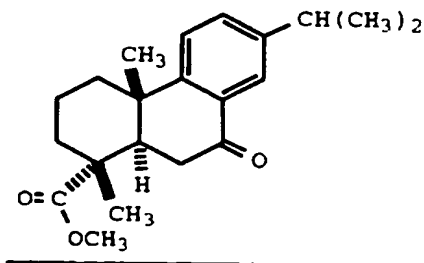
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To a solution of 112 mg (0.30 mmol) of the compound of
Example 4 in 4 ml of glacial AcOH and 1 ml of H_2O, was
added 10 mg (1.0 mmol) of chromium trioxide. The reaction
mixture was stirred at room temperature for 1 hour and then
5   partitioned between 50 ml of EtOAc and 50 ml of a saturated
NaCl solution. The resultant layers were separated and the
organic layer was dried over Na_2SO_4, filtered and then
concentrated in vacuo to provide a dark oil which was
purified using flash chromatography (eluent of 5% EtOAc in
10   hexanes) to provide an oil which solidified on standing.
Yield: 100 mg (90%).
IR (CHCl$_3$): 2965, 1722, 1675 and 1253 cm^{-1}.
^{1}H NMR (300MHz, CDCl$_3$): δ 7.88 (d, J=1.8Hz, 1H); 7.42 (dd,
J=1.8,8.1Hz, 1H); 7.30 (d, J=8.1Hz, 1H); 3.66 (s, 3H);
15   2.86-2.98 (m, 1H); 2.66-2.76 (m, 2H); 2.28-2.40 (m, 2H);
1.60-1.90 (m, 5H); 1.35 (s, 3H); 1.26 (s, 6H) and 1.24 (s,
3H).
MS(FD): m/e 329(M+).
Elemental Analysis for $C_{21}H_{28}O_3$:
20   Calcd: C, 76.79; H, 8.59;
            Found: C, 76.52; H, 8.53.

Example 6
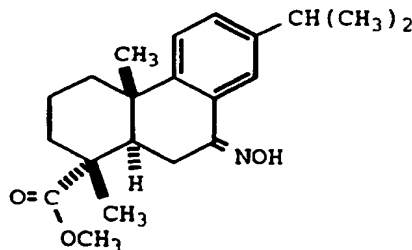
A mixture containing 118 mg (0.36 mmol) of the
compound of Example 5, 40 mg (0.58 mmol) of hydroxylamine
hydrochloride, 40 mg (0.48 mmol) of NaHCO$_3$, 1 drop of
glacial AcOH, 1.0 ml of H_2O and 15 ml of MeOH was refluxed
30   with a Dean-Stark trap for 5 hours. The reaction mixture
was concentrated in vacuo to provide a residue. This

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residue was partitioned between H_2O and CH_2Cl_2 and the organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude material was purified using flash chromatography.

5   Yield: 120 mg (97%).

IR(CHCl$_3$): 3582, 2962, 1721 and 1261 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ 7.71 (s, 1H); 7.43 (s, 1H); 7.21 (s, 2H); 3.66 (s, 3H); 2.85-2.95 (m,1H); 2.67 (m, 2H); 2.26-2.37 (m, 2H); 1.75 (m, 5H); 1.38 (s, 3H); 1.26 (s,

10   3H); 1.24 (s, 3H); 1.13 (s, 3H); MS(FD) m/e 343(M+).

Example 7
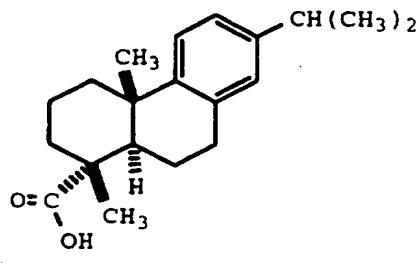
15   A mixture of 500 mg (1.59 mmol) of the compound of Example 3, 1.0 g (17.8 mmol) of KOH and 20 ml of n-butyl alcohol was refluxed for 16 hours, under N_2. After cooling, the mixture was acidified with 5N HCl and concentrated in vacuo to provide a residue. This residue

20   was suspended in 50 ml of H_2O and filtered. The resulting solid was dissolved in 50 ml of MeOH, filtered and the filtrate was concentrated in vacuo.

Yield: 330 mg of a foam (69%).

m.p. 143-145°C.

25   IR (KBr): 2958, 1695 and 1279 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ 7.25 (d, J=3Hz, 1H); 7.17 (d, J=8Hz, 1H); 7.00 (dd, J=3.9Hz, 1H); 6.89 (brs, 1H); 2.80-3.00 (m, 3H); 2.20-2.40 (m, 2H); 1.65-1.96 (m, 5H); 1.43-1.60 (m, 2H); 1.29 (s, 3H); 1.24 (s, 3H); 1.22 (s, 3H);

30   1.21 (s, 3H); MS(FD) m/e 301(M+).

Elemental Analysis for $C_{20}H_{28}O_2 \cdot 0.5H_2O$:

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Calcd: C, 79.01; H, 9.47;
Found: C, 79.19; H, 9.52.

Example 8
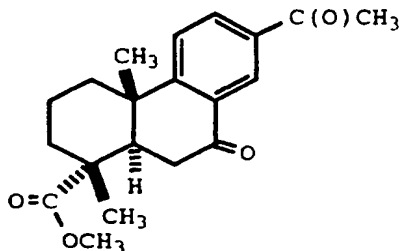
To a cold (0°C) solution of 8.0 g (25.0 mmol) of the compound of Example 3 in 50 ml of acetic anhydride and 38 ml of AcOH, was added 11.0 g (0.11 mmol) of chromium trioxide slowly, under N_2. The reaction mixture was partitioned between EtOAc and brine and the organic layer was dried over Na_2SO_4, filtered and concentrated to provide a yellow oil. This oil was purified using flash chromatography (SiO_2, eluent of 10% EtOAc in hexanes) to provide a solid which was filtered with the aid of hexanes. Yield: 2.5 g (30.5%).
m.p. 144-145°C.
IR (KBr):   2951, 1725 and 1680 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ 8.55 (d, J=2Hz, 1H); 8.17 (dd, J=2,8Hz, 1H); 7.50 (d, J=8Hz, 1H); 3.66 (s, 3H); 2.75 (m, 2H); 2.64 (s, 3H); 2.37-2.50 (m, 2H); 1.60-1.90 (m, 5H); 1.37 (s, 3H) and 1.29 (s, 3H).
MS(FD): m/e 328 (M+).
Elemental Analysis for $C_{20}H_{24}O_4$:
Calcd: C, 73.15; H, 7.37;
Found: C, 72.86; H, 7.42.

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Example 9

OC(O)CH₃

CH₃

O=C

OCH₃

CH₃

H

O
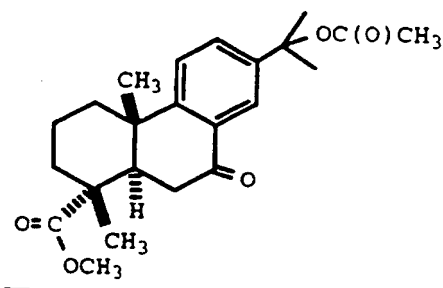
The compound was isolated from the reaction mixture described in Example 8.

Yield: 4.2 g of a white solid (43.5%).

m.p. 130-133°C.

IR (KBr): 2934, 1734, 1720 and 1680 cm⁻¹.

^{1}H NMR (300MHz, CDCl₃): δ7.98 (d, J=2Hz, 1H); 7.54 (dd, J=2,8Hz, 1H); 7.33 (d, J=8Hz, 1H); 3.66 (s, 3H); 2.75 (m, 2H); 2.30-2.42 (m, 2H); 2.2 (m, 1H); 2.04 (s, 3H); 2.00-2.10 (m, 1H); 1.70-1.90 (m, 3H); 1.76 (s, 6H); 1.35 (s, 3H) and 1.26 (s, 3H).

MS(FD): m/e 386 (M+).

Elemental Analysis for $C_{23}H_{30}O_5$:

Calcd: C, 71.48; H, 7.82;

Found: C, 71.75; H, 8.03.

Example 10

OH

CH₃

O=C

OCH₃

CH₃

H

O
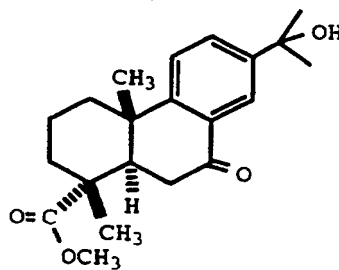
To a solution of 4.14 g (10.7 mmol) of the compound of Example 9 in 40 ml of MeOH, was added 13.4 ml (13.4 mmol) of 1N NaOH. The reaction mixture was refluxed for 2.5 hours, cooled and then partitioned between 200 ml of 0.2N HCl and 200 ml of EtOAc. The resultant layers were

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separated and the organic layer was washed with 200 ml of
brine, dried over Na_2SO_4, filtered and then concentrated in
vacuo to provide a dark yellow oil. This oil was purified
using flash chromatography (SiO_2, eluent of 15% EtOAc in

5   hexanes).
Yield: 2.9 g of a white foam (80%).
m.p. 57-60°C.
IR(KBr): 3444, 2936, 1727 and 1682 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ 8.06 (d, J=2.2Hz, 1H); 7.74 (dd,

10   J=2.2,8.5Hz, 1H); 7.36 (d, J=8.5Hz, 1H); 3.66 (s, 3H); 2.70
(m, 2H); 2.40 (m, 2H); 1.60-1.90 (m, 6H); 1.60 (s, 3H);
1.55 (s, 3H); 1.35 (s, 3H) and 1.27 (s, 3H).
MS(FD): m/e 344(M+).
Elemental Analysis for $C_{21}H_{28}O_4$:

15   Calcd: C, 73.23; H, 8.19;
         Found: C, 73.50; H, 8.46.

Example 11

20
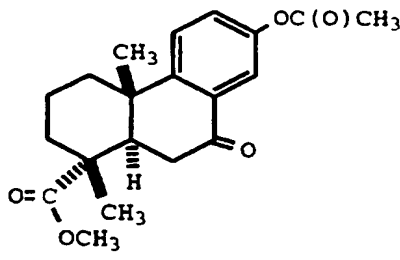
     A mixture of 500 mg (1.52 mmol) of the compound of
Example 8, 620 mg (1.80 mmol) of 50% m-chloroperbenzoic
acid, 5.0 mg (0.03 mmol) of p-toluene sulfonic acid
monohydrate and 5 ml of 1,2-dichloroethane was refluxed for

25   4 hours and then stirred overnight at room temperature.
The mixture was diluted with 25 ml of EtOAc and washed
sequentially with 25 ml of 10% potassium iodide, 10% sodium
thiosulfate, saturated $NaHCO_3$ and brine, dried over Na_2SO_4,
filtered and then concentrated in vacuo. The crude

30   material was purified by radial chromatography (eluent of

25% Et$_2$O in hexanes).

Yield: 30 mg (6%).

IR(CHCl$_3$): 3020, 1723 and 1684 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ7.69 (d, J=3Hz, 1H); 7.39 (d, J=9Hz, 1H); 7.24 (d, J=3Hz, 1H); 3.67 (s, 3H); 2.84 (m, 2H); 2.25-2.42 (m, 2H); 2.31 (s, 3H); 1.60-1.90 (m, 5H); 1.35 (s, 3H) and 1.28 (s, 3H).

MS(FD): m/e 344(M+).

Elemental Analysis for C$_{20}$H$_{24}$O$_5$:

    Calcd: C, 69.75; H, 7.02;
    Found: C, 69.77; H, 6.92.

Example 12
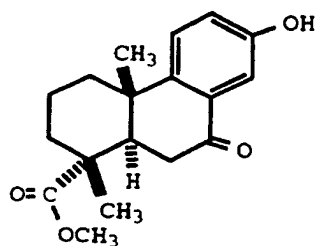
The compound was prepared substantially in accordance with the procedure detailed in Matsumoto et al., Bull. Chem. Soc. Jpn., vol. 61, pages 723-727 (1988), using the compound of Example 8.

Yield: 42%.

IR(CHCl$_3$): 3389, 2948, 1725, 1670, 1606 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ7.45 (d, J=3Hz, 1H); 7.27 (d, J=9Hz, 1H); 7.07 (dd, J=3,9Hz, 1H); 5.20 (s, 1H); 3.66 (s, 3H); 2.65-2.80 (m, 2H); 2.27-2.42 (m, 2H); 1.60-1.90 (m, 5H); 1.34 (s, 3H) and 1.25 (s, 3H).

MS(FD): m/e 302(M+).

Elemental Analysis for C$_{18}$H$_{22}$O$_4$:

    Calcd: C, 71.50; H, 7.33;
    Found: C, 71.22; H, 7.19.

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Example 13
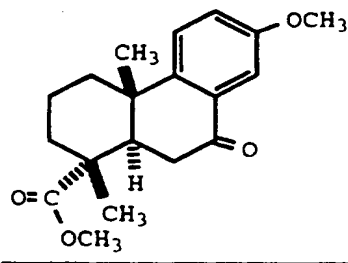
5   The compound was prepared substantially in accordance
with the procedure detailed in Matsumoto et al., Bull.
Chem. Soc. Jpn., vol. 61, 723-727 (1988), using the
compound of Example 12.
Yield: 86%.

10   IR(CHCl$_3$): 2941, 1722, 1677 and 1252 cm^{-1}.
^{1}H NMR (300MHz, CDCl$_3$): δ7.48 (d, J=3Hz, 1H); 7.29 (d,
J=9Hz, 1H); 7.11 (dd, J=3,9Hz, 1H); 3.84 (s, 3H); 3.66 (s,
3H); 2.70 (m, 2H); 2.30-2.43 (m, 2H); 1.60-1.90 (m, 5H);
1.34 (s, 3H) and 1.25 (s, 3H).

15   MS(FD): m/e 316(M+).
Elemental Analysis for C$_{19}$H$_{24}$O$_4$:
       Calcd: C, 72.13; H, 7.65;
       Found: C, 72.16; H, 7.35.

20   Example 14

       A.
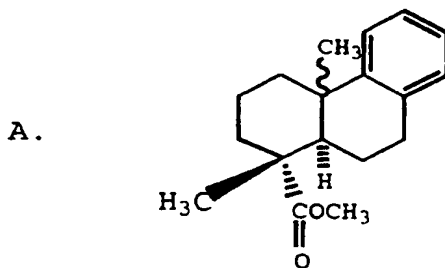
       A mixture of 475 mg (1.5 mmol) of the compound of
Example 3, 425 mg (3.19 mmol) of anhydrous aluminum
25   chloride in 15 ml of toluene was stirred at room

temperature for 2 hours, under N_2. The reaction mixture was partitioned between toluene and 1N HCl. The resultant layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to provide an oil. This oil was purified using flash chromatography (SiO_2, eluent of 2% EtOAc in hexanes) to provide an oil which was crystallized from MeOH .

^1H NMR (300MHz, $CDCl_3$): δ 7.00-7.30 (m, 4H); 3.30 (s, 1.5H); 3.28 (s, 1.5H); 2.90 (m, 2H); 2.30 (m, 2H); 2.00 (m, 1H); 1.40-1.80 (m, 6H); 1.30 (s, 1.5H); 1.22 (s, 3H) and 1.10 (s, 1.5H).

B.
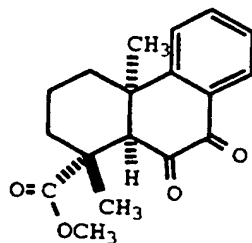
A solution of 285 mg (2.8 mmol) of chromium trioxide in 4 ml of glacial AcOH and 1 ml of H_2O was added dropwise to a solution of 275 mg (1 mmol) of the compound of Example 14A in 5 ml of glacial AcOH. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between EtOAc and brine (twice). The combined organic layers were dried over Na_2SO_4, filtered and then concentrated in vacuo to provide a yellow oil which was purified using flash chromatography (SiO_2, eluent of 5% EtOAc in hexanes).

Yield: 50 mg of a bright yellow solid (17%).

m.p. 121-123°C.

IR($CHCl_3$): 3019, 2954, 1727, 1688 and 1248 cm^{-1}.

^1H NMR (300MHz, $CDCl_3$): δ 8.14 (d, J=8Hz, 1H); 7.70 (7, J=7Hz, 1H); 7.47 (m, 2H); 3.73 (s, 3H); 3.39 (s, 1H); 2.64 (d, J=12Hz, 1H); 2.01-2.11 (m, 1H); 1.40-1.80 (m, 4H); 1.29 (s, 3H) and 0.69 (s, 3H).

MS(FD): m/e 300(M+).

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Elemental Analysis for $C_{18}H_{20}O_4$:
         Calcd: C, 71.98; H, 6.71;
         Found: C, 72.10; H, 6.66.

C.
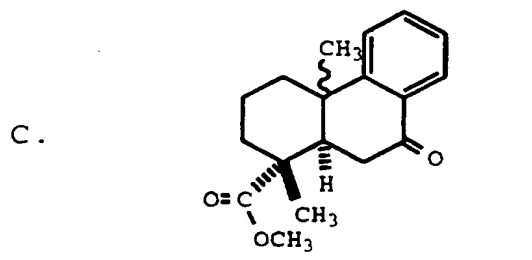
The compound was isolated Example 14B.
Yield: 136 mg of an oil (47.5%).
^{1}H NMR (300MHz, CDCl$_3$): δ 8.01 (m, 1H); 7.55 (m, 1H); 7.30
(m, 2H); 3.30 (s, 1.5H); 3.28 (s, 1.5H); 3.10 (dd,
J=4,12Hz, 0.5H): 2.70 (m, 1.5H); 2.40 (m, 2H); 1.40-1.90
(m, 5H); 1.30 (s, 1.5H); 1.28 (s, 1.5H); 1.23 (s, 1.5H);
0.65 (s, 1.5H).

Example 15

A.
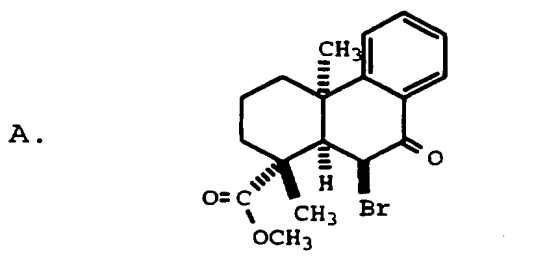
A solution of 0.9 ml (17 mmol) of bromine in 30 ml of
anhydrous Et$_2$O was added to a solution of 3.8 g (13.3 mmol)
of the compound of Example 14C in 200 ml of anhydrous Et$_2$O,
dropwise. The reaction mixture was stirred at room
temperature for 1 hour and then washed sequentially with
H$_2$O, a saturated NaHCO$_3$ solution and 19% sodium thiosulfate,
dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to
provide a residue. This residue was purified using flash
chromatography (eluent of 3:2 CH$_2$Cl$_2$/hexanes).
Yield: 1.2 g of yellowish oil (25%).

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^{1}H NMR (300MHz, CDCl$_3$):   δ 8.00 (dd, J=2,5Hz, 1H); 7.60 (dt, J=2,5Hz, 1H); 7.40 (m, 2H); 4.60 (s, 1H); 3.78 (s, 3H); 3.25 (s, 1H) 2.50 (d, J=7Hz, 1H); 1.60-1.90 (m, 5H); 1.60 (s 3H); 0.57 (s, 3H).

B.
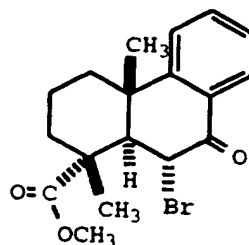
The compound was isolated from Example 15A.
Yield: 1.2 g of an oil (25%).
^{1}H NMR (300MHz, CDCl$_3$):   δ 8.01 (d, J=6Hz, 1H); 7.60 (m, 1H); 7.40 (m, 2H); 5.00 (d, J=9Hz, 1H); 3.65 (s, 3H); 3.23 (d, J=9Hz, 1H); 2.60 (m, 1H); 2.38 (d, J=7Hz, 1H); 1.80 (m, 4H); 1.52 (s, 3H) and 1.25 (s, 3H).

Example 16

A.
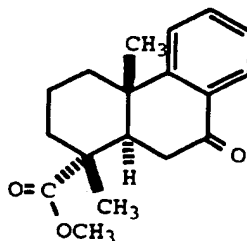
A mixture of 960 mg (2.6 mmol) of the compound of Example 15B, 4.0 g (61.2 mmol) of zinc dust, 2.0 g (24.4 mmol) of NaOAc and 50 ml of glacial AcOH was refluxed for 1 hour, under N$_2$. After cooling, the reaction mixture was filtered and the filtrate was partitioned between Et$_2$O and brine. The resultant layers were separated and the organic layer was dried over Na$_2$SO$_4$, filtered and then concentrated in vacuo. The crude material was purified using flash chromatography (SiO$_2$, eluent of 10% Et$_2$O in hexanes).
Yield: 500 mg of an oil (67.2%).

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IR(CHCl$_3$): 3028, 1722, 1679, 1258 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ 8.01 (d, J=8Hz, 1H); 7.54 (7, 6Hz, 1H); 7.29 (m, 2H); 3.67 (s, 3H); 2.74 (dd, J=3,7Hz, 2H); 2.30-2.45 (m, 2H); 1.60-1.90 (m, 5H); 1.36 (s, 3H) and 1.28 (s, 3H).

MS(FD): m/e 286(M+).

B.
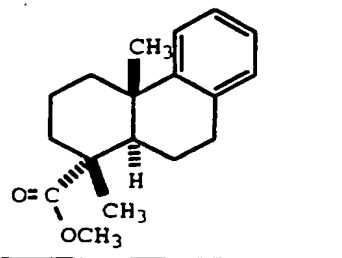
The compound was isolated from Example 16A. Yield: 150 mg (21%).

Example 17

A.
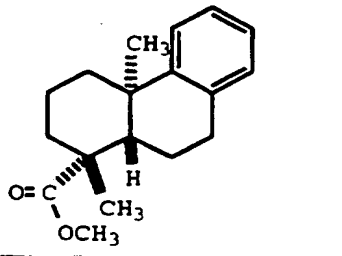
A solution of 1.54 g (5.66 mmol) of the compound of Example 14A and 1.5 g of 10% Pd/C in 150 ml of triethyleneglycol dimethyl ether was refluxed for 3 hours, under N$_2$. After cooling, the mixture was filtered and the filtrate was partitioned between EtOAc and brine (three times). The resultant layers were separated and the combined organic layers were dried over Na$_2$SO$_4$, filtered and the concentrated in vacuo to provide 1.5 g of a residue. A fraction of this residue (300 mg) was purified by chromatotron (eluent of 2% CH$_2$Cl$_2$ in hexanes initially, followed by the addition to the mobile phase of 50 ml of

- 40-

CH_2Cl_2 after 200 ml elution, and finally 4 ml of EtOAc after 300 ml had eluted).

Yield: 29 mg

^{1}H NMR (300MHz, CDCl$_3$): δ 7.00-7.30 (m, 4H); 3.63 (s, 3H); 2.83 (m, 2H); 2.30 (m, 3H); 2.00 (m, 2H); 1.30-1.70 (m, 3H); 1.25 (s, 3H); 1.10 (m, 1H); 1.02 (s, 3H).
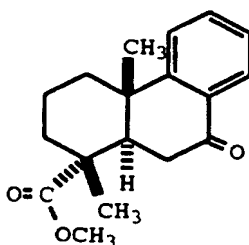
B. A mixture of

and
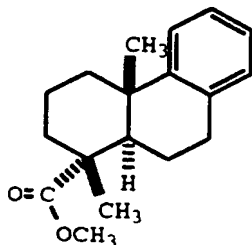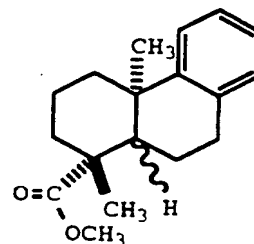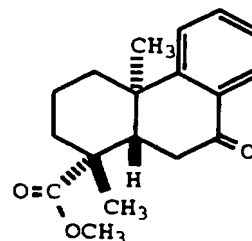
The compounds were isolated from Example 17A.

Yield: 216 mg.
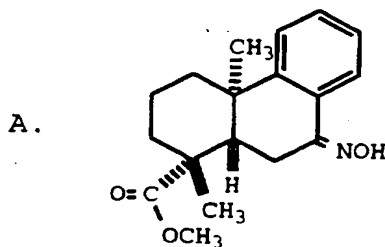
Example 18

A. A mixture of

and

The compounds were prepared substantially in accordance with the procedure detailed in Example 14B, using a solution of 325 mg (1.2 mmol) of the unpurified residue from Example 17A in 5 ml of glacial AcOH The crude material was purified using flash chromatography (SiO$_2$, eluent of 15% Et$_2$O in hexanes).

Yield: 62 mg of an oil.

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Example 19

A.

5   The compound was prepared substantially in accordance
with the procedure detailed in Example 6, using a solution
containing 140 mg (0.49 mmol) of the compounds of Example
18A in 10 ml of MeOH. The crude material was purified
using flash chromatography (SiO$_2$, eluent of 20% Et$_2$O in
10   hexanes).
Yield: 38 mg of a solid (26%).
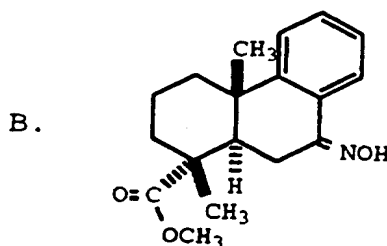m.p. 139-141°C.
IR(CHCl$_3$): 3584, 3020 and 1720 cm^{-1}.
^{1}H NMR (300MHz, CDCl$_3$): δ 7.92 (d, J=7.7Hz, 1H); 7.56 (s,
15   1H); 7.30 (m, 2H); 7.20 (m, 1H); 3.72 (s, 3H); 3.44 (dd,
J=4.0,18.4Hz, 1H); 3.12 (dd, J=14.0,18.7Hz, 1H); 2.35 (m,
2H); 2.03 (m, 1H); 1.50-1.80 (m, 3H); 1.32 (s, 3H); 1.10
(m, 1H) and 1.02 (s, 3H).
MS(FD): m/e 301(M+).
20   Elemental Analysis for C$_{18}$H$_{23}$NO$_3$:
           Calcd: C, 71.74; H, 7.69; N, 4.65;
           Found: C, 71.97; H, 7.77; N, 4.39.

B.

25·   The compound was isolated from Example 19A.
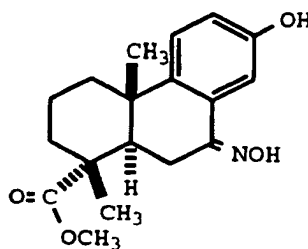   Yield: 38 mg of a resin (26%).

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IR(CHCl₃):   3583, 3027, 2935, 1721 and 1263 cm⁻¹.

¹H NMR (300MHz, CDCl₃):   δ 7.85 (d, J=8.1Hz, 1H); 7.43 (s, 1H); 7.10-7.20 (m, 3H); 3.66 (s, 3H); 2.67 (d, J=8.8Hz, 2H); 2.28-2.37 (m, 2H); 1.76 (m, 4H); 1.39 (s, 3H); 1.26 (m, 1H) and 1.14 (s, 3H).

MS(FD):   m/e 301(M+).

Example 20

The compound was prepared substantially in accordance with the procedure detailed in Example 6, using the compound of Example 12.

IR(KBr):   3393, 2932, 1727 and 1702 cm⁻¹.

¹H NMR (300MHz, CDCl₃):   δ 8.00 (brs, 1H); 7.29 (d, J=3Hz, 1H); 7.16 (d, J=9Hz, 1H); 6.85 (dd, J=3,9Hz, 1H); 5.25 (brs, 1H); 3.68 (s, 3H); 2.65 (m, 2H); 2.20-2.40 (m, 2H); 1.55-2.04 (m, 5H); 1.40 (s, 3H) and 1.10 (s, 3H).

MS(FD):   m/e 318(M+).

Elemental Analysis for C₁₈H₂₃O₄:

    Calcd: C, 68.12; H, 7.30; N, 4.41;

    Found: C, 67.95; H, 7.46; N, 4.12.

Example 21
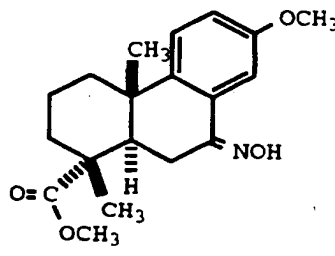
- 43-

The compound was prepared substantially in accordance with the procedure detailed in Example 6, using the compound of Example 13.

Yield: 93%.

5   IR(KBr): 3421, 2936, 1727 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ7.37 (d, J=3Hz, 1H); 7.29 (s, 1H); 6.92 (d, J=9Hz, 1H); 6.91 (dd, J=3,9Hz, 1H); 3.81 (s, 3H); 3.66 (s, 3H); 2.65 (m, 2H); 2.25-2.65 (m, 2H); 1.60-1.80 (m, 5H); 1.38 (s, 3H) and 1.11 (s, 3H).
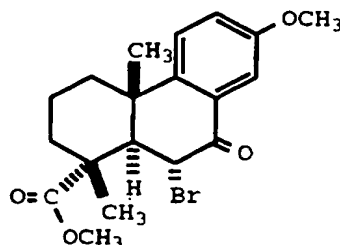
10 MS(FD): m/e 331(M+).

Elemental Analysis for C$_{19}$H$_{25}$NO$_4$:

        Calcd: C, 68.86; H, 7.60; N, 4.23′
        Found: C, 69.10; H, 7.83; N, 4.23.

15   Example 22

The compound was prepared substantially in accordance with the procedure detailed in Example 15A, using the

20 compound of Example 13.

Yield: 74%

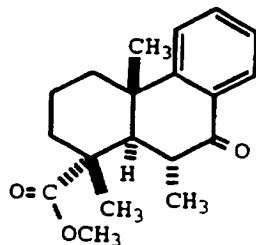m.p. 146-148°C.

IR(KBr): 2900, 1725 and 1679 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ7.46 (d, J=3Hz, 1H); 7.28 (d,

25 J=9Hz, 1H); 7.14 (dd, J=3,9Hz, 1H); 4.98 (d, J=13Hz, 1H); 3.85 (s, 3H); 3.65 (s, 3H); 3.20 (d, J=13Hz, 1H); 2.35 (m, 1H); 1.70-1.90 (m, 5H); 1.50 (s, 3H); 1.26 (s, 3H).

MS(FD): m/e 397 (M+).

Elemental Analysis for C$_{19}$H$_{23}$BrO$_4$:

30   Calcd: C, 57.73; H, 5.86;
        Found: C, 57.78; H, 6.06.

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Example 23

5   To a stirring solution of 70 mg (0.245 mmol) of the
compound of Example 16A in 20 ml of anhydrous THF, was
added 32 mg (0.80 mmol) of 60% NaH on mineral oil, under
N_2. The resultant mixture was stirred 15 minutes followed
by the addition of 0.15 ml (2.25 mmol) of iodomethane, via
10   syringe. The reaction mixture was stirred for 3 hours,
quenched by the dropwise addition of H_2O and then
partitioned between Et_2O and H_2O. The resultant layers were
separated and the organic layer was dried over Na_2SO_4,
filtered and concentrated in vacuo to provide a residue
15   which was purified by radial chromatography (eluent of 10%
Et_2O in hexanes).

Yield: 16 mg of a clear oil (22%).
IR(CHCl$_3$): 3692, 3022, 2950, 1724 and 1678 cm^{-1}.
^{1}H NMR (300MHz, CDCl$_3$): δ7.95 (d, J=7.7Hz, 1H); 7.54 (s,
20   J=8.8Hz, 1H); 7.25 (m, 2H); 3.63 (s, 3H); 2.80 (m, 2H);
2.39 (d, J=7.7Hz, 1H); 1.70-2.05 (m, 5H); 1.43 (s, 3H);
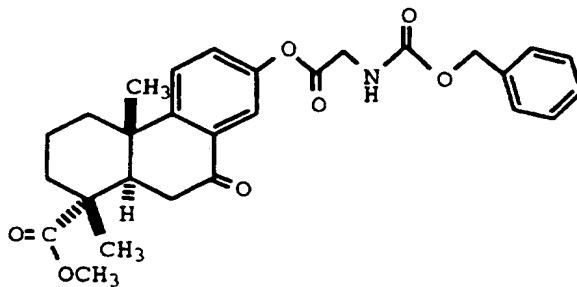1.28 (s, 3H) and 1.13 (d, J=6.2Hz, 3H).
MS(FD): m/e 300 (M+).
Elemental Analysis for $C_{19}H_{24}O_3$:
25   Calcd: C, 75.97; H, 8.05;
         Found: C, 75.80; H, 7.96.

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Example 24

5   A mixture of 50 mg (0.165 mmol) of the compound of
Example 12, 35 mg (0.165 mmol) of carbobenzyloxyglycine, 35
mg (0.170 mmol) of 1,3-dicyclohexylcarbodiimide (DCC), 2 mg
(0.0165 mmol) of 4-dimethylaminopyridine in 25 ml of
anhydrous Et_2O was stirred for 16 hours resulting in the
10   formation of a solid. This solid was removed by filtration
and the filtrate was washed sequentially with H_2O, a 5%
AcOH solution and brine. The combined organic layers were
dried over Na_2SO_4, filtered and then concentrated in vacuo
to provide a resin. This resin was purified using flash
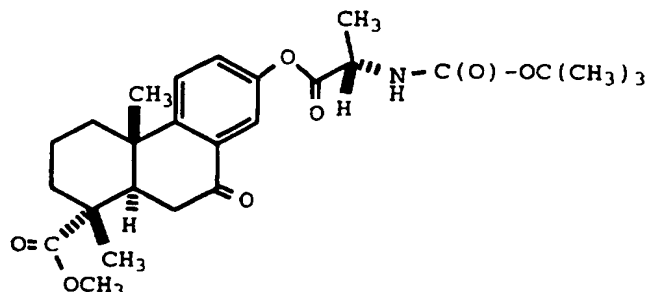15   chromatography (SiO_2, eluent of 20% Et_2O in hexanes).
Yield: 54 mg of a light yellow solid (66%).
IR(KBr): 3330, 2934, 1779, 1725, 1685 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$): δ7.70 (s, 1H); 7.36 (m, 8H); 6.20
(s, 2H); 4.26 (d, J=6Hz, 2H); 3.67 (s, 3H); 2.73 (dd,
20   J=3,6Hz, 2H); 2.40 (m, 2H); 1.50-2.00 (m, 5H); 1.35 (s,
3H); 1.28 and (s, 3H).
MS(FD): m/e 494 (M+).

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Example 25

5   The compound was prepared substantially in accordance
with the procedure detailed in Example 24, using the
compound of Example 12 and N-t-butoxycarbonyl-L-alanine .
Yield: 96%.
IR(CHCl₃):   3444, 2938, 1763, 1714 cm⁻¹.
10   ¹H NMR (300MHz, CDCl₃):   δ7.69 (d, J=2.6Hz, 1H); 7.41 (d,
J=8.5Hz, 1H); 7.30 (d, J=2.6Hz, 1H); 5.10 (brm, 1H); 4.55
(brm, 1H); 3.65 (s, 3H); 2.73 (dd, J=3.3, 6.6Hz, 2H); 2.32-
2.42 (m, 2H); 1.70-2.20 (m, 5H); 1.55 (d, J=7.0Hz, 3H);
1.47 (s, 6H); 1.43 (s, 3H); 1.35 (s, 3H) and 1.28 (s, 3H).
15   MS(FD):   m/e 474 (M+).

Example 26
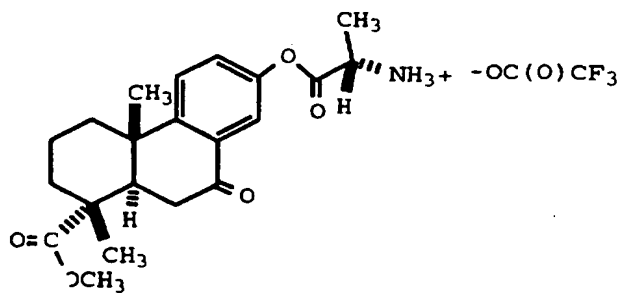
20   A mixture of 100 mg (0.21 mmol) of the compound of
Example 25 in 2 ml of CH₂Cl₂ was added to 2 ml of a 1:1
CH₂Cl₂/CF₃COOH mixture. After stirring for 1 hour, the
reaction mixture was concentrated in vacuo. The resultant
residue was concentrated repetitively in Et₂O until a foam
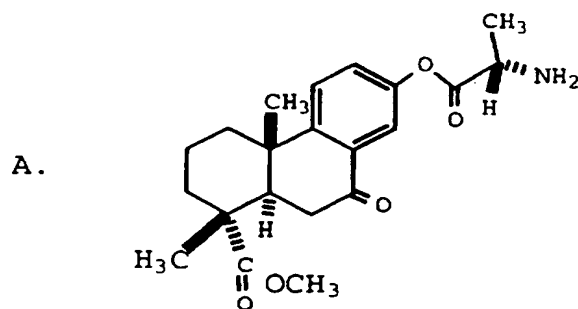25   was obtained.

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Yield: 85 mg (83%).

IR(CHCl$_3$):   2941, 1715, 1711 and 1682 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$):   δ7.65 (m, 2H); 7.41 (d, J=8.1Hz,
1H); 4.30 (m, 1H); 3.62 (s, 3H); 2.63 (m, 2H); 2.25-2.40
(m, 2H); 1.60-1.90 (m, 5H); 1.34 (s, 3H) and 1.24 (s, 3H);
1.22 (d, J=7.0Hz, 3H).

MS(FD):   m/e 374, free base (M+).

<u>Example 27</u>

A.

To a solution of 550 mg (1.0 mmol) of the compound of
Example 25 in 10 ml of CH$_2$Cl$_2$, was added 3 ml (39 mmol) of
CF$_3$COOH.   After stirring for 1 hour, the reaction mixture
was concentrated in vacuo to provide a foam.   This foam was
dissolved in 20 ml of CH$_2$Cl$_2$ followed by the addition of
0.17 ml (1.2 mmol) of Et$_3$N.   The resultant layers were
separated and the organic layer was washed with H$_2$O, dried
over Na$_2$SO$_4$, filtered and concentrated in vacuo to provide a
foam.
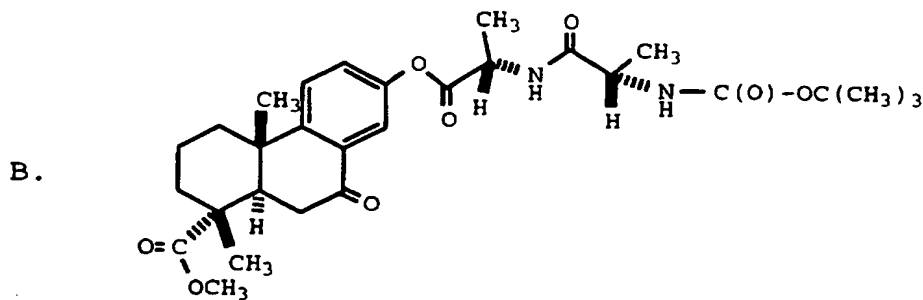
B.

The compound was prepared substantially in accordance
with the procedure detailed in Example 24, using the

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compound of Example 27A and 230 mg (1.2 mmol) of N-t-butyloxycarbonyl-L-alanine

Yield: 255 mg (47%).

IR(KBr):   3334, 2938, 1770, 1725 and 1687 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ7.69 (d, J=3Hz, 1H); 7.41 (d, J=9Hz, 1H); 7.29 (d, J=3Hz, 1H); 6.70 (m, 1H); 5.00 (m, 1H); 4.80 (m, 1H); 4.20 (m, 1H); 3.67 (s, 3H); 2.73 (m, 2H); 2.36 (m, 2H); 1.60-1.90 (m, 5H); 1.58 (d, J=7Hz, 3H); 1.45 (s, 9H); 1.38 (d, J=7Hz, 3H); 1.35 (s, 3H) and 1.27 (s, 3H).
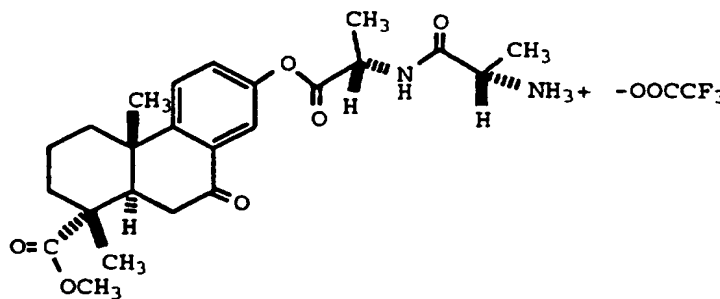
MS(FD):   m/e 544 (M+).

Elemental Analysis for C$_{29}$H$_{40}$N$_2$O$_8$·0.75H$_2$O:

    Calcd: C, 62.40; H, 7.43; N, 5.02;
    Found: C, 62.30; H, 7.24; N, 4.77.

Example 28

The compound was prepared substantially in accordance with the procedure detailed in Example 26, using the compound of Example 27B.
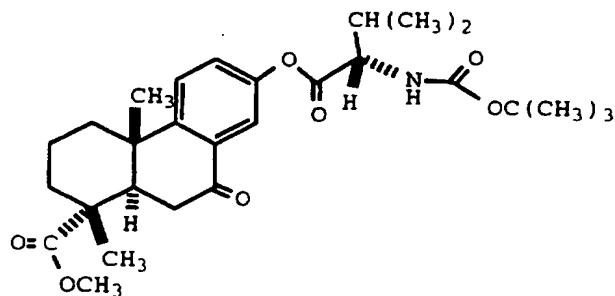
Yield: 95%..

IR(KBr):   2950, 1770 and 1681 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ8.17 (brs, 3H); 7.60 (s, 1H); 7.40 (d, J=2.6Hz, 1H); 7.27 (m, 1H); 4.65 (brs, 1H); 4.40 (brs, 1H); 3.70 (d, J=2Hz, 1H); 3.62 (s, 3H); 2.70 (m, 7H); 2.35 (m, 2H); 1.50-1.85 (m, 6H); 1.32 (s, 3H) and 1.23 (s, 3H).

MS(FD):   m/e 445 free base (M+).

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Example 29

5   The compound was prepared substantially in accordance
with the procedure detailed in Example 24, using the
compound of Example 12 and N-t-butoxycarbonyl-L-valine.
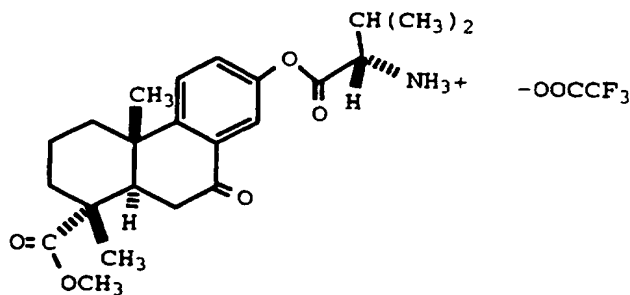Yield: 47%.

IR(KBr): 3377, 2969, 1766, 1724 and 1688 cm^{-1}.

10   ^{1}H NMR (300MHz, CDCl$_3$): δ 7.68 (d, J=2.6Hz, 1H); 7.41 (d,
J=8.8Hz, 1H); 7.29 (d, J=2.6Hz, 1H); 5.06 (brm, 1H); 4.45
(brm, 1H); 3.65 (s, 3H); 2.74 (dd, J=3.3,7.0Hz, 2H); 2.30-
2.43 (m, 1H); 1.70-1.90 (m, 6H); 1.48 (s, 9H); 1.35 (s,
3H); 1.28 (s, 3H); 1.09 (d, J=6.6Hz, 3H); 1.02 (d, J=7.0Hz,

15   3H).

MS(FD): m/e 502 (M+).

Elemental Analysis for C$_{28}$H$_{39}$NO$_7$:

          Calcd: C, 67.04; H, 7.84; N, 2.79;
          Found: C, 66.82; H, 7.73; N, 2.58.

20

Example 30

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The compound was prepared substantially in accordance
with the procedure detailed in Example 26, using the
compound of Example 29.

Yield: 99% yield.

IR(KBr): 3068, 2943, 1758, 1722 and 1668 cm^{-1}.

^{1}H NMR (300MHz, CDCl$_3$): δ7.68 (m, 1H); 7.40 (m, 2H); 4.08
(d, J=4.8Hz, 1H); 3.65 (s, 3H); 2.70 (m, 2H); 2.30-2.40 (m,
2H); 1.70-1.90 (m, 6H); 1.34 (s, 3H); 1.26 (s, 3H); 1.16
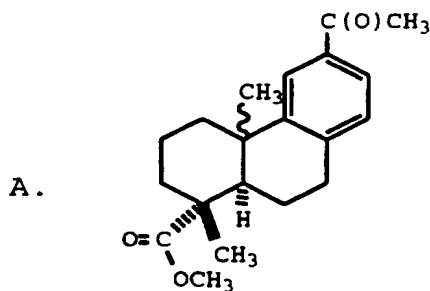(d, J=2.9Hz, 3H) and 1.14 (d, J=2.9Hz, 3H).

MS(FD): m/e free base 402 (M+).

Elemental Analysis.for C$_{25}$H$_{32}$NO$_7$:

        Calcd: C, 58.25; H, 6.26; N, 2.72;

   Found: C, 57.98; H, 6.32; N, 2.64.

Example 31

A.

A mixture of 4.0 g (14.7 mmol) of the compound of
Example 14A and 1.2 ml (16.9 mmol) of acetyl chloride in 60
ml of carbon disulfide to a suspension of 2.6 mg (19.5
mmol) of anhydrous aluminum chloride in 100 ml of carbon
disulfide, via dropping funnel. The reaction mixture was
refluxed for 1 hour and then the carbon disulfide was
removed by downward distillation. The resultant residue
was cautiously quenched by the addition of 100 ml of 0.2N
HCl. The desired compound was extracted using 100 ml of
CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered and then concentrated in
vacuo to provide a dark red oil. This oil was purified
using flash chromatography (SiO$_2$, eluent of 20% Et$_2$O in
hexanes).

Yield: 1.7 g of an oil (87% based on recovered starting material).

^{1}H NMR (300MHz, CDCl$_3$):   δ7.90 (d, J=4Hz, 1H); 7.75 (d, J=4Hz, 0.5H); 7.63 (d, J=4Hz, 0.5H); 7.37 (d, J=6Hz, 0.5H); 7.10 (d, J=6Hz, 0.5H); 3.70 (s, 1.5H); 3.68 (s, 1.5H); 2.92 (m, 2H); 2.60 (s, 3H); 2.00-2.50 (m, 3H); 1.40-1.98 (m, 6H); 1.29 (s, 1.5H); 1.26 (s, 1.5H); 1.24 (s, 1.5H) and 1.10 (s, 1.5H).

B.
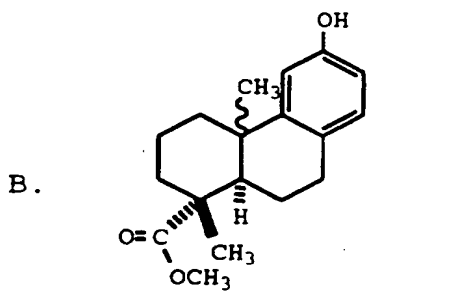
A mixture of 1.7 g (5.4 mmol) of the compound of Example 31A, 1.9 g (5.5 mmol) of 50% 3-chloroperoxybenzoic acid, 18 mg (0.095 mmol) of p-toluene sulfonic acid monohydrate in 25 ml of 1,2-dimethyoxyethane was refluxed for 3 hours, under N$_2$. After cooling, the reaction mixture was diluted with Et$_2$O and washed sequentially with 10% potassium iodide, 10% sodium thiosulfate, a saturated NaHCO$_3$ solution and brine, dried over Na$_2$SO$_4$, filtered and then concentrated to provide a resin which was dissolved in 25 ml of MeOH and 10 ml of H$_2$O containing 1.6 g (19.0 mmol) of NaHCO$_3$. The mixture was refluxed for 1.5 hours, cooled, filtered and concentrated in vacuo to provide a residue which was partitioned between H$_2$O and Et$_2$O. The resulting layers were separated and the organic layer was washed sequentially with 1N HCl and brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo

Yield: 1.55 g (99%).

^{1}H NMR (300MHz, CDCl$_3$):   δ6.85 (m, 1H); 6.70 (d, J=6Hz, 1H); 6.55 (dd, J=6Hz, 1H); 3.63 (s, 3H); 2.80 (m, 2H); 1.90-2.30 (m, 3H); 1.40-1.88 (m, 6H); 1.25 (s, 1.5H); 1.20 (s, 1.5H); 1.17 (s, 1.5H) and 1.02 (s, 1.5H).

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C.
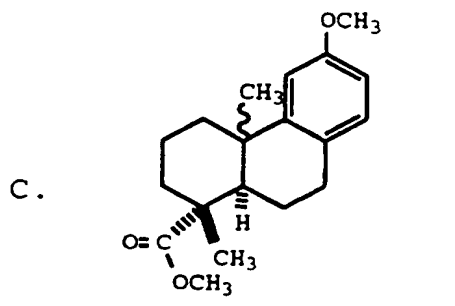
To a suspension of 1.55 g (5.4 mmol) of the compound
of Example 31B and 275 mg (6.87 mmol) of 60% NaH on mineral
oil in 50 ml of anhydrous DMF, was added 0.5 ml (7.50 mmol)
of idodomethane, under N_2. The reaction mixture was
stirred for 1 hour and then cautiously quenched by the
dropwise addition of brine. The reaction mixture was
partitioned between Et_2O and brine. The resultant layers
were separated and the organic layer was dried over Na_2SO_4,
filtered and concentrated in vacuo to provide a residue
which was purified using flash chromatography (SiO_2, eluent
of 20% Et_2O in hexanes).

Yield: 1.3 g of a clear light yellow oil (88.5% based on
recovered starting material).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.00 (d, J=6Hz, 1H); 6.82 (m,
1H); 6.70 (m, 1H); 3.80 (s, 3H); 3.70 (s, 3H); 2.80 (m,
2H); 2.00-2.40 (m, 3H); 1.40-1.90 (m, 6H); 1.25 (s, 1.5H);
1.20 (s, 3H); 1.10 (s, 1.5H).

Note: The reaction mixture also contained 200 mg of the
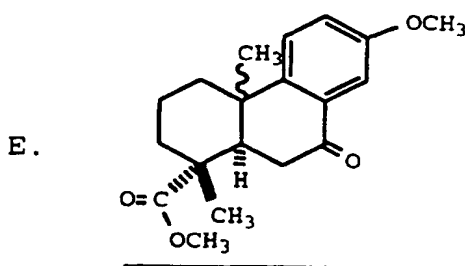compound of Example 31A.
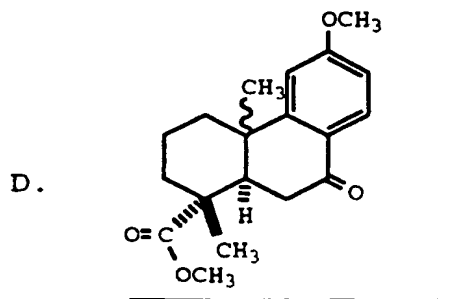
D.

The compound was prepared substantially in accordance
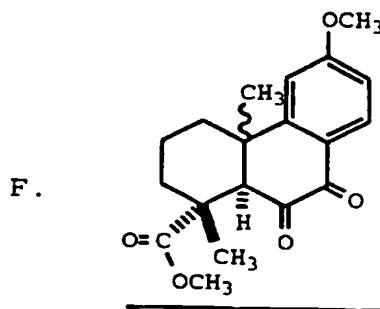with the procedure detailed in Example 14B, using 1.3 g

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(4.3 mmol) of the compound of Example 31C. The crude
material was purified using flash chromatography (SiO$_2$,
eluent of 20% Et$_2$O in hexanes).

Yield: 820 mg of an oil (60.5%).

^{1}H NMR (300MHz, CDCl$_3$):   δ 8.00 (m, 1H); 6.80 (m, 2H); 3.87
(s, 1.5H); 3.85 (s, 1.5H); 3.63 (s, 1.5H); 3.61 (s, 1.5H);
3.01 (dd, J=5, 12Hz, 0.5H); 2.70 (m, 1.5H); 2.40 (m, 2H);
1.40-1.95 (m, 5H); 1.32 (s, 1.5H); 1.30 (s, 1.5H); 1.22 (s,
1.5H); 0.65 (s, 1.5H).

E.

The compound was isolated from Example 31D.
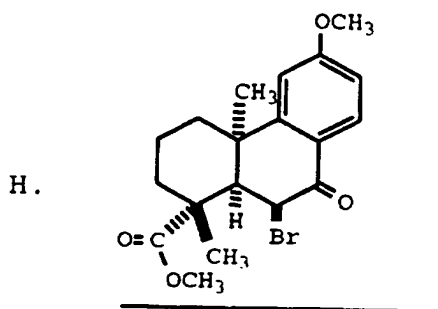Yield: 35.4 mg of an oil.

F.

The compound was isolated from Example 31D.
Yield: 150 mg of an oil (10.6%).

^{1}H NMR (300MHz, CDCl$_3$):   δ 8.17 (d, J=6Hz, 1H); 6.95 (m,
1H); 6.80 (m, 1H); 3.90 (s, 3H); 3.70 (s, 3H); 3.36 (s,
0.5H); 2.50 (m, 1.5H); 1.80-2.10 (m, 1H); 1.42-1.80 (m,
4H); 1.40 (s, 1.5H); 1.20 (s, 1.5H); 1.17 (s, 1.5H); 0.65
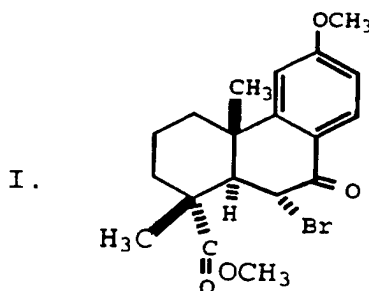(s, 1.5H).

Example 31G-deleted

H.

The compound was prepared substantially in accordance with the procedure detailed in Example 15A, using 975 mg (3.08 mmol) of the compound of Example 31D. The crude material was purified using flash chromatography (SiO$_2$, eluent of 15% of Et$_2$O in hexanes).

Yield: 532.6 mg (44%).

^{1}H NMR (300MHz, CDCl$_3$):   δ 8.03 (d, J=6Hz, 1H); 6.81 (m, 2H); 4.50 (s, 1H); 3.90 (s, 3H); 3.75 (s, 3H); 3.21 (s, 1H); 2.40 (m, 1H); 1.60-2.00 (m, 5H); 1.58 (s, 3H) and 0.60 (s, 3H).
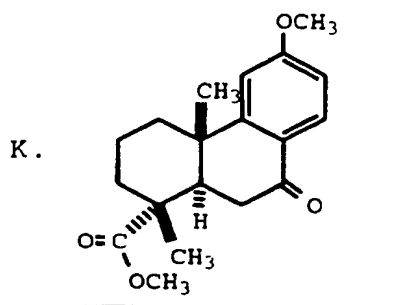

I.

The compound was isolated from Example 31H.

Yield: 465.1 mg of an oil (38%).

^{1}H NMR (300MHz, CDCl$_3$):   δ 8.00 (d, J=6Hz, 1H); 6.85 (m, 2H); 4.97 (d, J=9Hz, 1H); 3.90 (s, 3H); 3.62 (s, 3H); 3.22 (d, J=9Hz, 1H); 2.30 (m, 1H); 1.80 (m, 5H); 1.48 (s, 3H) and 1.28 (s, 3H).

Example 31J-deleted

- 55-

K.

The compound was prepared substantially in accordance
with the procedure detailed in Example 16, using 465 mg
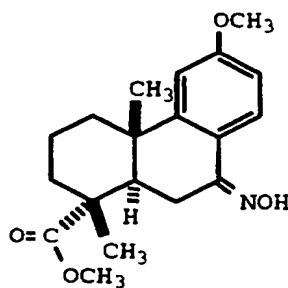(1.17 mmol) of the compound of Example 31I.
Yield: 328 mg of a clear oil (89%).
IR(CHCl$_3$): 2942, 1721, 1667 and 1596 cm^{-1}.
^{1}H NMR (300MHz, CDCl3): δ 8.01 (d, J=9.2Hz, 1H); 6.85 (s,
1H); 6.81 (d, J=2.6Hz, 1H); 3.90 (s, 3H); 3.66 (s, 3H);
2.70 (m, 2H); 2.30 (m, 2H); 1.60-1.90 (m, 5H); 1.35 (s, 3H)
and 1.26 (s, 3H).
MS(FD): m/e 316 (M+).

Example 32

The compound was prepared substantially in accordance
with the procedure detailed in Example 6, using the
compound of Example 31K.
Yield: 61%.
m.p. 162-165°C.
IR(CHCl$_3$): 3018, 2951, 1720 and 1600 cm^{-1}.
^{1}H NMR (300MHz, CDCl3): δ 7.81 (d, J=6Hz, 1H); 6.82 (m,
3H); 3.90 (s, 3H); 3.70 (s, 3H); 2.62 (d, J=6Hz, 2H); 2.20-
2.43 (m, 2H); 1.60-1.90 (m, 5H); 1.40 (s, 3H) and 1.10 (s,
3H).

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MS(FD):   m/e 331 (M+).
Elemental Analysis for $C_{19}H_{25}NO_4$:
       Calcd: C, 68.86; H, 7.60; N, 4.23;
       Found: C, 68.79; H, 7.42; N, 4.33.

5

       As noted above, the compounds of the present invention
are useful for inhibiting an envelope virus that undergoes
hemagglutinin-mediated fusion with a host cell. Thus, the
claimed compounds may be used to treat or prevent a viral
10   infection where the virus is an envelope virus that
undergoes hemagglutinin-mediated fusion which comprises
administering to an virus-infected cell, a cell susceptible
to infection or a mammal in need thereof an effective
amount of a compound of formula I or a pharmaceutically
15   acceptable salt thereof. The claimed compounds may also be
used to inhibit viral replication in an envelope virus that
undergoes hemagglutinin-mediated fusion which comprises
administering to a virus-infected cell, a cell susceptible
to infection or a mammal in need thereof, an effective
20   amount of a compound of formula I or a pharmaceutically
acceptable salt thereof.
       The term "effective amount" as used herein, means an
amount of a compound of the present invention which is
capable of inhibiting the hemagglutinin mediated fusion of
25   the virus with the host cell. The inhibition contemplated
by the present method includes both therapeutic and
prophylactic treatment, as appropriate. The specific dose
of compound administered according to this invention to
obtain therapeutic and/or prophylactic effects will, of
30   course, be determined by the particular circumstances
surrounding the case, including, for example, the compound
administered, the route of administration, the condition
being treated and the individual being treated. A typical
daily dose (administered in single or divided doses) will
35   contain a dosage level of from about 0.01 mg/kg to about
50 mg/kg of body weight of an active compound of this
invention. Preferred daily doses generally will be from

about 0.05 mg/kg to about 20 mg/kg and ideally from about
0.1 mg/kg to about 10 mg/kg.

The compounds can be administered by a variety of
routes including oral, rectal, transdermal, subcutaneous,
5   intravenous, intramuscular and intranasal. The compounds
of the present invention are preferably formulated prior to
administration. Therefore, another embodiment of the
present invention is a pharmaceutical formulation
comprising an effective amount of a compound of formula I
10   or a pharmaceutically acceptable salt thereof and a
pharmaceutically acceptable carrier, diluent or excipient
therefor.

The active ingredient in such formulations comprises
from 0.1% to 99.9% by weight of the formulation. By
15   "pharmaceutically acceptable" it is meant that the carrier,
diluent or excipient is compatible with the other
ingredients of the formulation and not deleterious to the
recipient thereof.

The present pharmaceutical formulations are prepared
20   by known procedures using known and readily available
ingredients. In making the compositions of the present
invention, the active ingredient will usually be admixed
with a carrier, or diluted by a carrier, or enclosed within
a carrier which may be in the form of a capsule, sachet,
25   paper or other container. When the carrier serves as a
diluent, it may be a solid, semi-solid or liquid material
which acts as a vehicle, excipient or medium for the active
ingredient. Thus, the compositions can be in the form of
tablets, pills, powders, lozenges, sachets, cachets,
30   elixirs, suspensions, emulsions, solutions, syrups,
aerosols, (as a solid or in a liquid medium), ointments
containing, for example, up to 10% by weight of the active
compound, soft and hard gelatin capsules, suppositories,
sterile injectable solutions, sterile packaged powders and
35   the like.

The following experiments were carried out to demonstrate the ability of the compounds of the present invention to inhibit influenza.

5

In vitro CPE/XTT Assay

MDCK cells were dispersed in a microtiter plate (96 wells) at 10,000 cells per well with Medium 199 containing Earl's balanced salt solution (EBSS), 1% fetal bovine serum (FBS), penicillin (100 units/ml) and

10 streptomycin (100 μg/ml). After standing overnight at 37°C in a carbon dioxide (CO_2) incubator, the MDCK cells were infected with ~0.1 moi (mutiplicity of infection) of influenza virus (i.e. A/Kawasaki/89 or B/Hong Kong and B/Great Lakes) at 0.03 moi. After allowing the virus to

15 adsorb to the cells for 1-2 hours, medium containing serial dilutions of drug or medium alone was added to the wells. The resultant mixtures were incubated for 2-3 days (until extensive cpe was apparent in medium alone wells). The antiviral effect of a test compound was assessed by

20 performing the following XTT assay.

A fresh solution (0.4 mg/ml) of XTT [2,3-bis(methoxy-4-nitro-5-sulfophenyl)-2H-tetraazolium-5-carboxanilide, inner salt, sodium salt] in warm medium without FBS was prepared. For each 5 ml of the XTT solution, 25 μl of 5mM PMS

25 (phenazine methosulfate) in phosphate buffer saline was added. After withdrawing the cultured supernatant, 100 μl of the freshly prepared XTT/PMS mixture was added to each of the microtiter wells. The wells were then incubated at 37°C (under CO_2) for 3-4 hours or until color change is prominent.

30 The absorbance at 450 nm (ref. 650 nm) was read in a spectrophotometer. The concentration of test compound required to cause 50% cytotoxic effect (TC_{50}) relative to a control with no drug and no virus present and which inhibits the development of virus cytopathic effect (cpe) by 50%

35 (IC_{50}) or 90% (IC_{90}) was determined from the linear portion of each dose response curve.

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Using this CPE/XTT assay, the IC_{50} of the compounds of formula I was determined to be in the range of 1.0-2.4 µg/ml for influenza A/Kawasaki/89 and in the range of 8-47 µg/ml for influenza B/Lee.

5

Plaque Reduction Assay

Susceptible MDCK cells were grown in 6 well tissue culture treated cluster plates at 1×10^6 cells/well in Minimum 199 with 1 percent fetal bovine serum, penicillin
10 (100 units/ml) and streptomycin (100 µg/ml). After overnight incubation at 37°C, the growth medium was removed and 0.2 ml/well of an appropriate dilution of virus was added. After adsorption for 1-2 hour at room temperature, the infected cell sheet was overlaid with equal parts of
15 1.5% sterile agarose solution.and a twofold concentration of medium 199 (with 2% fetal bovine serum, 100 units/ml of penicillin and 100 µg/ml streptomycin) containing varying concentrations of compounds.

The compounds were dissolved in DMSO at a
20 concentration of 20 mg/ml and an aliquot was diluted to the desired concentration in DMSO and then added to the agar medium mixture. The plates were incubated in a CO_2 incubator at 37°C until the DMSO control wells contained plaques of optimal size. Then, a solution containing 10
25 percent formalin and 2 percent sodium acetate was added to each well to inactivate the virus and fix the cell sheet to the plastic surface. The fixed cell sheets were stained with 0.5 percent crystal violet and the plaques were counted. Results from duplicate wells at each
30 concentration were averaged and compared with DMSO control wells. The inhibition of plaque formation by 50 or 90 percent (IC_{50} or IC_{90}) was calculated from the linear region of the inhibition concentration curve using the method of Reed and Muench, Am. J. Hyg., vol. 27, pages 493-497
35 (1958).

- 60-

Using this plaque reduction assay, the IC_{50} of the compounds of formula I was determined to be in the range of 0.02-100 μg/ml for influenza A/Kawasaki and was determined to be in the range of 1.5-60.5 μg/ml for influenza B/Lee.
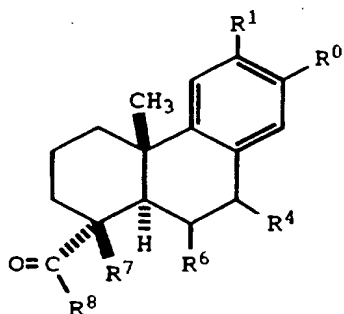
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We claim:

    1.   A compound of the formula:

        I

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wherein:

    R^0 and R^1 are independently hydrogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6 alkyl), sulfhydryl, sulfamyl, $-SO_2-Cl$, $-S-C(O)-N(CH_3)_2$, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, C_1-C_4 alkylsulfonylamino, di(C_1-C_4 alkylsulfonyl)amino $-X^0-O-C(O)-C_1-C_4$ alkyl, $-O-(X^1)_i-X^2$, $-C(O)-X^3$, $-N-C(O)-R^2$ or $-O-R^3$;

    X^0 is a bond or divalent(C_1-C_6 alkyl);
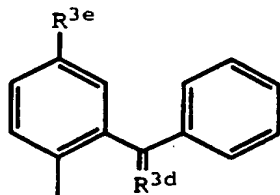
    X^1 is an amino acid;

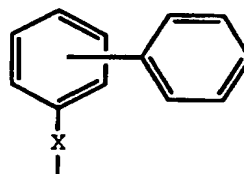 X^2 is hydrogen or an amino protecting group;

    i is 1, 2 or 3;

    X^3 is C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6 alkyl), hydroxy(C_1-C_6 alkyl) or phenyl;

    R^2 is C_1-C_4 alkyl, C_1-C_4 alkoxy, halo(C_1-C_4 alkyl), hydroxy(C_1-C_4 alkyl), phenyl, p-methoxy-phenyl, p-fluoro-phenyl, naphthyl, pyridyl, piperidinyl, thiazolyl, oxazolyl, thienyl, furyl, tetrahydrofuryl or cyclohexyl;

    R^3 is C_1-C_6 alkenyl, $-CH_2-R^{3a}$, $-C(O)-R^{3b}$, $-C(S)-R^{3c}$, $-C(CH_3)_2C(O)NH_2$, phenyl or a group of the formula:

     or   ;

R^{3a} is phenyl, p-fluorophenyl, pyridyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, N-(C_1-C_4 alkoxycarbonyl)piperidinyl, N-(trifluoromethyl)-piperidinyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, isooxazolyl, quinolyl, isoquinolyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, cyclohexyl, cyclopentyl, cyclopropyl or naphthyl;

R^{3b} is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, N-(C_1-C_4 alkoxycarbonyl)piperidinyl, N-(trifluoromethyl)piperidinyl, benzyloxy, pyridylmethyloxy, C_1-C_6 alkoxy, halo(C_1-C_4 alkoxy), amino, C_1-C_4 alkylamino or di(C_1-C_4 alkyl)amino;

R^{3c} is amino, C_1-C_4 alkylamino or di(C_1-C_4 alkyl)amino;

R^{3d} is oxygen, hydroximino, hydrazino or =CHZ;

Z is hydrogen, C_1-C_4 alkyl, halogen, di(C_1-C_4 alkyl)amino, C_1-C_4 alkoxycarbonyl, carbamoyl(C_1-C_4 alkyl), N-(C_1-C_4 alkyl)carbamoyl or N,N-di(C_1-C_4 alkyl)carbamoyl;

R^{3e} is hydrogen, nitro or trifluoromethyl;

X is a bond or -(CH_2)-;

R^4 is hydrogen, hydroxy, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, C_1-C_4 alkoxy, =O, -O-S(CH_3)$_2$C(CH_3)$_3$, C_2-C_6 alkanoyloxy, N-(C_2-C_6 alkanoyl)amino, =N-R^5 or R^4 and R^6 combine to form a bond;

R^5 is hydroxy, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, C_1-C_4 alkoxy, pyridylmethoxy, benzyloxy, piperazinyl, N-(methyl)piperazinyl or -O-CH_2-C(O)-R^{5a};

R^{5a} is hydroxy or C_1-C_4 alkoxy;

R^6 is hydrogen, halo, C_1-C_4 alkyl or =O;

R^7 is hydrogen or C_1-C_4 alkyl;

R^8 is hydroxy, halo, C_1-C_6 alkoxy, pyrrolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, morpholinyl or -N(R^9)-R^{10};

R^9 is hydrogen or methyl;

R^{10} is -(divalent C_1-C_6 alkyl)-R^{10a};

R^{10a} is pyridyl,

with the proviso that

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i) when R^4 is hydrogen or =O; R^8 is methoxy; and R^1 is hydrogen; then R^0 cannot be hydrogen, hydroxy, isopropyl, methoxy, $-C(CH_3)_2OH$, $-C(O)CH_3$ or $-OC(O)CH_3$;

ii) when R^4 is hydrogen or =O; R^8 is methoxy; and R^0 is isopropyl; then R^1 cannot be hydroxy or methoxy;

iii) when R^4 is hydrogen or =O; R^8 is hydroxy; and R^0 is hydrogen; then R^1 cannot be hydrogen or isopropyl;

iv) when R^4 is hydrogen; R^8 is methoxy; and R^0 is hydrogen; then R^1 cannot be hydrogen, hydroxy, $-C(O)CH_3$ or $-OC(O)CH_3$;

or a pharmaceutically acceptable salt thereof.

2.   A compound according to claim 1 where:

R^0 is hydrogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6 alkyl), $-X^0$-O-$C(O)$-C_1-C_4 alkyl, $-O$-$(X^1)_i$-X^2, $-C(O)$-X^3 or $-O$-R^3;

R^1 is hydrogen, hydroxy, C_1-C_6 alkoxy, sulfhydryl, sulfamyl, $-SO_2$-Cl, amino, di(C_1-C_4 alkylsulfonyl)amino, $-C(O)$-X^3, $-N$-$C(O)$-R^2 or $-O$-R^3;

X^0 is a bond or divalent(C_1-C_6 alkyl);

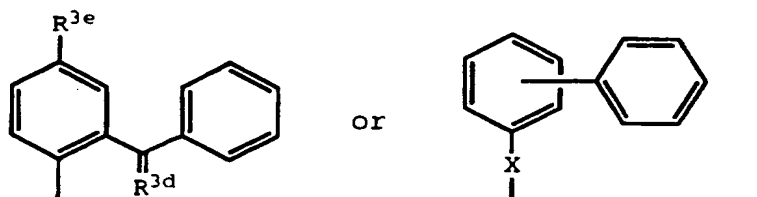X^1 is an amino acid;

X^2 is hydrogen or an amino protecting group;

i is 1 or 2;

X^3 is C_1-C_6 alkyl;

R^2 is hydroxy(C_1-C_4 alkyl);

R^3 is C_1-C_6 alkenyl, $-CH_2$-R^{3a}, $-C(O)$-R^{3b}, $-C(S)$-R^{3c}, $-C(CH_3)_2C(O)NH_2$ or a group of the formula:

R^{3a} is phenyl, p-fluorophenyl, pyridyl, piperidinyl, piperazinyl or morpholinyl;

R^{3b} is piperidinyl, piperazinyl, morpholinyl, N-$(C_1-C_4$ alkoxycarbonyl)piperidinyl, N-(trifluoromethyl)piperidinyl, halo(C_1-C_4 alkoxy) or di(C_1-C_4 alkyl)amino;

R^{3c} is di(C_1-C_4 alkyl)amino;

R^{3d} is oxygen or hydroximino;

R^{3e} is hydrogen, nitro or trifluoromethyl;

X is a bond;

R^4 is hydrogen, hydroxy, amino, =O, C_2-C_6 alkanoyloxy, =N-R^5 or -OSi$(CH_3)_2$;

R^5 is hydroxy, amino, di(C_1-C_4 alkyl)amino, C_1-C_4 alkoxy, pyridylmethoxy, N-(methyl)piperazinyl or -O-CH_2-C(O)-R^{5a};

R^6 is hydrogen, chloro, bromo, methyl or =O;

R^7 is hydrogen or methyl;

R^8 is hydroxy, chloro, methoxy, 4-methylpiperazinyl or -N(R^9)-R^{10};

R^9 is hydrogen;

R^{10} is -CH_2-R^{10a}; and

R^{10a} is pyridyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 where:

R^0 is hydrogen, hydroxy, C_1-C_6 alkoxy, -O-$(X^1)_i$-X^2, -X^0-O-C(O)-C_1-C_4 alkyl or -O-R^3;

R^1 is hydrogen, hydroxy, C_1-C_6 alkoxy or -O-R^3;

X^0 is a bond;

X^1 is an amino acid;

X^2 is hydrogen or an amino protecting group;

i is 1 or 2;

R^3 is C_1-C_6 alkenyl, -CH_2-R^{3a} or -C(O)-R^{3b};

R^{3a} is p-fluorophenyl or pyridyl;

R^{3b} is piperidinyl;

R^4 is hydrogen, hydroxy, =O or =N-R^5;

R^5 is hydroxy, dimethylamino or N-(methyl)piperazinyl;

R^6 is hydrogen, bromo or =O;

R^7 is methyl; and

R^8 is methoxy;

or a pharmaceutically acceptable salt thereof.

4.   A compound according to claim 3 where:

5   R^0 is hydrogen, hydroxy, C_1-C_4 alkoxy, $-O-(X^1)_i-X^2$,

$-O-C(O)$methyl or $-O-R^3$;

R^1 is hydrogen, hydroxy, C_1-C_4 alkoxy or $-O-R^3$;

X^1 is glycine, alanine or valine;

X^2 is hydrogen, t-butoxycarbonyl or benzyloxycarbonyl;

10   R^4 is =O or =N-R^5;

R^5 is hydroxy;

R^6 is hydrogen;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :CO7C 69/76, 271/24 ; CO7D 211/06, 295/185, 207/32
US CL :544/155, 381; 546/203, 204; 548/539; 560/21, 28, 51, 65, 64, 102

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/155, 381; 546/203, 204; 548/539; 560/21, 28, 51, 65, 64, 102

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,276,053 (JOHNSON) 04 January 1994, col. 6, formula I, lines25-65.	1-4
A	US 5,321,044 (PETERS et al) 14 June 1994, col. 3,4,5 and 6, entire disclosure in these columns.	1-4

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
		"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 JUNE 1997	1 2 AUG 1997

Name and mailing address of the ISA/US	Authorized officer
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(74) Agents: MCCLAIN, Janet, T. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

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Published
With international search report.

(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract

The present invention provides compounds which inhibit an envelope virus by inhibiting the fusion of the virus with the host cell. The virus may be inhibited in an infected cell, a cell susceptible of infection or a mammal in need thereof.